A Dissertation on

DETECTION OF ASYMPTOMATIC SPONTANEOUS BACTERIAL PERITONITIS IN CIRRHOTIC PATIENTS WITH ASCITES

Dissertation Submitted to

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for the award of the degree of

M.D. GENERAL MEDICINE

BRANCH-I

COIMBATORE MEDICAL COLLEGE,

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CERTIFICATE

Certified that this is the bonafide dissertation done by ***Dr.JOE FRANCIS MATHEW*** *and submitted inpartial fulfillment of the requirements for the Degree of* ***M.D.,General Medicine,*** *Branch I of* ***The Tamilnadu DR. M.G.R.Medical University Chennai.***

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DECLARATION

I solemnly declare that the dissertation titled **"Detection of asymptomatic Spontaneous Bacterial Peritonitis in cirrhotic patients with Ascites."** Was done by me from JULY 2014 to JULY 2015 under. The guidance and supervision of Professor **Dr.M.RAVEENDRAN M.D.**

This dissertation is submitted to **The Tamilnadu Dr. M.G.R. Medical University** towards the partial fulfillment of the requirement for theaward of MD Degree in General Medicine (Branch I).

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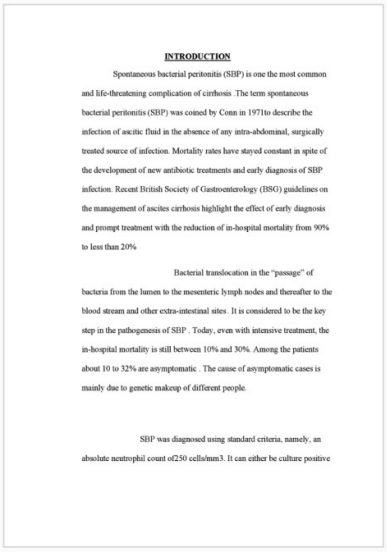
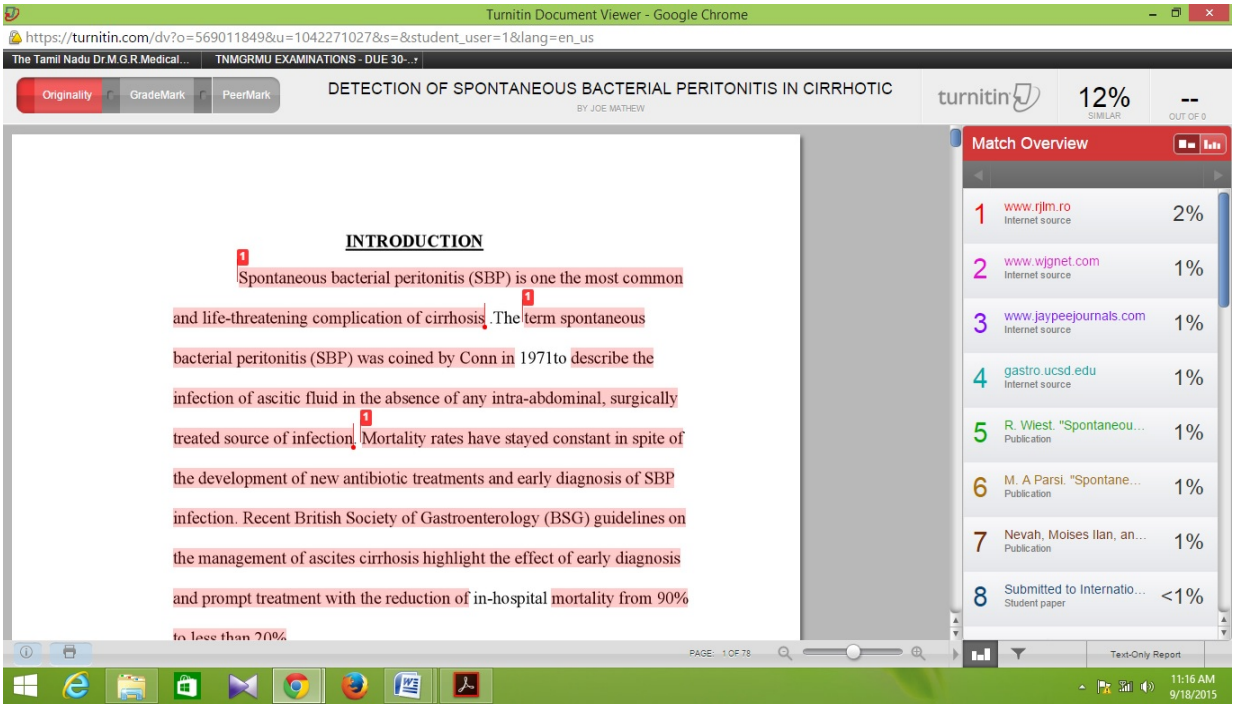


INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is one the most common and life-threatening complication of cirrhosis .The term spontaneous bacterial peritonitis (SBP) was coined by Conn in 1971to describe the infection of ascitic fluid in the absence of any intra-abdominal, surgically treated source of infection. Mortality rates have stayed constant in spite of the development of new antibiotic treatments and early diagnosis of SBP infection. Recent British Society of Gastroenterology (BSG) guidelines on the management of ascites cirrhosis highlight the effect of early diagnosis and prompt treatment with the reduction of in-hospital mortality from 90% to less than 20%

Bacterial translocation in the "passage" of bacteria from the lumen to the mesenteric lymph nodes and thereafter to the blood stream and other extra-intestinal sites .It is considered to be the key step in the pathogenesis of SBP . Today, even with intensive treatment, the in-hospital mortality is still between 10% and 30%. Among the patients about 10 to 32% are asymptomatic . The cause of asymptomatic cases is mainly due to genetic makeup of different people.

SBP was diagnosed using standard criteria, namely, an absolute neutrophil count of250 cells/mm3. It can either be culture positive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Place : Coimbatore Dr . JOE FRANCIS MATHEW

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ABBREVIATION

1. SBP – Spontaneous Bacterial Peritonitis
2. CNNA - Culture Negative Neutrocytic Ascites
3. INR – International Normalised Ratio
4. TIPS – Transjugular Intrahepatic Portal Systemic shunt
5. UKELD – United Kingdom Model End stage Liver Disease
6. MELD – Modified End stage Liver Disease
7. PT – Prothrombin Time
8. US FDA – United States Food and Drug Administration
9. RAAS – Renin Angiotensin Aldosterone System
10. ADH – Anti Diuretic Hormone
11. SAAG – Serum Ascites Albumin Gradient
12. PMN – Poly morphonuclear cells
13. EDTA – Ethylene Diamine Tetra Acetic acid
14. NSAID – Non Steroidal Anti Inflammatory Drug
15. LVP – Le Veen Peritoneal shunt
16. HE – Hepatic Encephalopathy
17. VATS – Video Assisted Thoracoscopy
18. TNF – Tumour Necrosis Factor
19. IL – Interleukin
20. MNB – MonomicrobialNonneutrocyticBacterascites
21. CT – Computed Tomography

22. MRI - Magnetic Resonance Imaging
23. UGI – Upper Gastro Intestinal
24. HRS – Hepatorenal Syndrome
25. SIBO – Small Intestine Bacterial Overgrowth
26. AASLD – American Association for the Study of Liver Disease
27. MRSA – Methicillin Resistant Staphylococcal Aureus
28. USG – Ultrasonogram

INTRODUCTION

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Bacterial translocation in the "passage" of bacteria from the lumen to the mesenteric lymph nodes and thereafter to the blood stream and other extra-intestinal sites . It is considered to be the key step in the pathogenesis of SBP . Today, even with intensive treatment, the in-hospital mortality is still between 10% and 30%. Among the patients about 10 to 32% are asymptomatic . The cause of asymptomatic cases is mainly due to genetic makeup of different people.

SBP was diagnosed using standard criteria, namely, an absolute neutrophil count of 250 cells/mm3. It can either be culture positive or culture negative. If ascitic fluid cultures were negative in the presence of neutrocytic ascites, these patients were characterized as having culture-negative neutrocytic ascites (CNNA). Patients with positive cultures on asciticfluid but without neutrocytic ascites were classified as having bacterascites.

AIM

To detect the prevalence of asymptomatic Spontaneous Bacterial Peritonitis in Cirrhotic patients with ascites and treat them prior to complication .

OBJECTIVES

1. Early detection of Spontaneous Bacterial Peritonitis in Cirrhotic patients with Ascites who do not have classical symptoms of the same .
2. To intervene in positive cases prior to onset of complication .

REVIEW OF LITERATURE

Spontaneous bacterial peritonitis (SBP) as the name suggests is the infection of the ascitic fluid in the absence of a contiguous intra-abdominal infection and source of inflammation like cholecystitis and pancreatitis[1].In spite of advanced development in antibiotic field and hospital care , the mortality of spontaneous bacterial peritonitis is still high . Recent guidelines put forward by the British Society of Gastroenterology (BSG) which throws light on the importance of early diagnosis and prompt diagnosis has shown the reduction of hospital mortality from 90% to 20 %[2].

A brief look out to the history reveals that Conn and Fessel coined the term Spontaneous Bacterial Peritonitis back in 1971 as they noticed infected fluid in cirrhotic patients [3].Another pioneer whose name needs mention is Runyon who noticed several mysterious death in the pre SBP era [4].

The prevalence of SBP in hospitals is said to be between 10 % to 30% [5].Prior to the development of antibiotics the inpatient mortality of SBP was as high as 90 %.Patients at risk of developing spontaneous bacterial peritonitis are those with active variceal bleed, ascites protein less than 10g/dl and with a prior history of SBP.

The prevalence of Asymptomatic SBP is even less and it still stays as a grey area in literatures . For an infection to be asymptomatic as the word denotes , the patient must be free of any symptoms of infection which is mainly

fever .A study conducted in 1994 by the Mayo Clinic Division of Gastroenterology and Hepatology showed that the prevalence was very low . The various other factors taken into consideration are absence of features of hepatic encephalopathy , abdominal tenderness , upper gastrointestinal bleeding and deterioration of renal function .Another study conducted by the Military Hospital , Rawalpindi Pakistan in 2008 also states that the incidence of asymptomatic SBP is as low as 5 % . Yet another study by Cadranel JF et al also states that the incidence is low and exploratory paracentesis can be avoided in such patients without significant risk. It is also seen that asymptomatic SBP has a less severe disease outcome . The mortality rate of asymptomatic SBP is also low compared to symptomatic .

By definition Spontaneous Bacterial Peritonitis is an absolute neutrophil count of more than 250 cells /mm^3 which is neutrocytic ascites in the absence of intra abdominal source of infection[6] . If ascitic fluid culture is positive and the neutrophil count is 250cells/mm3, such patients are diagnosed as culture-positive neutrocytic ascites. If ascitic fluid culture is negative in the presence of neutrocytic ascites, these patients are characterized as having culture-negative neutrocytic ascites (CNNA). Patients with positive cultures on ascitic fluid but without neutrocytic ascites are classified as having bacterascites.

But in some instances like in hemorrhagic ascites or traumatic tapping , a calculation adjustment has to be thought of to account for the presence of blood in the fluid .One polymorphonuclear cell is subtracted for every 250 red

blood cells . By this method, the sensitivity of the diagnostic paracentesis is increased .

ANATOMY OF PERITONEAL CAVITY

The peritoneal cavity is a thin, serous, continuous glistening membrane lining the abdominal & pelvic walls and clothing the abdominal and pelvic viscera. The potential space between the two layers is filled with very thin film of serous fluid to facilitate the movement of the abdominal organs. It is the largest cavity in the body .Its main function is to lubricate the serous layer of the organs and support the viscera. Greater omentum is called the policeman of abdomen to prevent spread of infection.It secretes the peritoneal fluid.It is considered to be having a surface area of 0.55 m^2 to 2 m^2 with the cavity to body surface area ratio of 0.6 to 0.8 .

PORTAL VEIN

Formed behind the neck of pancreas by the union of superior mesenteric vein and splenic vein. Ascends upwards and to the right, posterior to the first part of duodenum and then enters the lesser omentum to the porta hepatis, where it divides into right and left branches .There are no functioning valves in hepatic portal system .It drains rains blood from gastrointestinal tract from the lower end of oesophagus to the upper end of anal canal, pancreas, gall bladder, bile ducts and spleen. The various tributaries of portal vein are Superior mesenteric vein, Inferior mesenteric vein, Splenic vein, Left gastric

vein, Right gastric vein, Cystic vein and the Paraumbilical vein. There are various sites of porto systemic and porto retroperitoneal anastomosis. They are

1.At the lower end of esophagus

2.At rectal venous plexus

3.At periumbilical venous plexus

The pathophysiology of esophageal varices formation due to portal hypertension is made clear by this anatomy . As massive hematemesis per say is a sole cause for spontaneous bacterial peritonitis , prompt treatment of esophageal varices plays a key role in prevention of SBP.

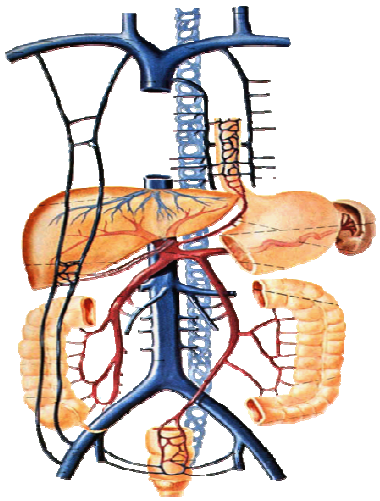


Figure 1 . Various sites of Portocaval anastomosis .

CIRRHOSIS OF LIVER

Cirrhosis is a condition of liver where it slowly looses its integrity and function by chronic injury to the tissue. Liver is the largest organ of the human body and it weighs around 3 pounds. Due to chronic injury the normal liver tissue is replaced by the scar tissue which hinder the blood flow through the liver . In the initial period inspite of scar tissue accumulation , liver continues to work but gradually the cells starts to lose its function which culminates in hepatic failure. Cirrhosis is considered to be the 12^{th} leading cause of death in the world [7]

Various etiologies has been attributed to cirrhosis . Chronic alcoholism and hepatitis infection is considered to be most common causes [8].Non alcoholic fatty liver disease [NAFLD] is an upcoming life style epidemic as it races with the other causes of cirrhosis of liver . Other rare causes of cirrhosis includes autoimmune hepatitis , biliary atresia , cystic fibrosis ,primary biliary cirrhosis , primary sclerosing cholangitis and a rare entity called as Alagille syndrome characterised by loss of biliary function in infancy due to digestive disorder . The symptoms of cirrhosis is very vague which include – easy fatiguability, weight loss , loss of appetite , itching and edema of legs .

Diagnosis of cirrhosis can be done under a 5 faceted approach

1. History
2. Physical examination
3. Blood test

4. Imaging
5. Tissue biopsy

Some of the scoring systems used to assess the prognosis of cirrhosis of liver includes the

1. Model End - stage Liver Disease [MELD] score which takes into account the serum bilirubin, creatinine and INR. If serum sodium is also taken into consideration, it is known as UKELD . It was initial taken as a guideline for a three month mortality score in post TIPS patients. Later on it was used to determine prognosis and prioritizing the patients for liver transplant

   It is given by the formula

MELD = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43×aetiology(0: cholestatic or alcoholic, 1: otherwise)

2. Child Pugh's score that helps in planning the outcome of liver transplant and mortality which also takes into account bilirubin, ascites ,INR, albumin level and presence of encephalopathy .

   It was initially used to calculate prognosis of chronic liver disease but now it has gained interest in knowing the strength of the treatment and the need for liver transplant.

Measure	1 point	2 points	3 points
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
Prothrombin time, prolongation (secs)	<4.0	4.0-6.0	> 6.0
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

The interpretation is as follows

Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Another important prognostic factor for the liver disease is the Maddrey's discrimant factor . A score of more than 32 indicates an in hospital 1 month mortality in 35 to 45 %.It is given by the formula

4.6 x (PT test - control))+ S.Bilirubin in mg/dl

Imaging techniques used in diagnosing cirrhosis of liver includes an ultrasound, computed tomography, magnetic resonance imaging and elastography. Elastography is considered to be the gold standard for cirrhosis detection .Liver biopsy is also considered as a test for cirrhosis .

Complications of cirrhosis liver includes portal hypertension , ascites with the sequalae of spontaneous bacterial peritonitis , splenomegaly , esophageal varices , hepatic encephalopathy and gall bladder disorders .

Hepatic encephalopathy

Hepatic encephalopathy is considered as one of the most life threatening complication of fulminant hepatic failure . It is defined as a serious complication of chronic liver disease characterised by alteration of mental status and cognitive function . It is seen in 50 to 70 % 0f patients with cirrhosis and is considered as a poor prognostic factor . the projected 1 year survival rate is 46% and 3 year survival rate is 23% without liver transplant . Gut derived neurotoxins shunt to the brain due to ineffective detoxification of liver is the key of pathophysiology . Ammonia is considered to be the prime important chemical to be involved. It is said that the arterial ammonia level is raised in upto 90 % of patients with Hepatic Encephalopathy . The increase in the permeability of the blood brain barrier with accumulation of the ammonia which leads to astrocyte swelling and defective transport of neuro active elements like myoinositol are considered to be the pathophysiology behind this complication .Estimation of serum ammonia is always elevated .The normal value is 150 to 200 µg /dl .

Changes in mental status is the typical clinical finding along with altered sleep rhythm i.e day time solemnness . Severe brain edema leading to cerebral herniation is a feared complication . Certain precipitating factors are seen to

play a pivotal role in the triggering of encephalopathy. Constipation, dehydration , infection, upper gastrointestinal bleed and hypokalemia are some of it .

Asterixis, a finding in hepatic encephalopathy is caused due to the inability to maintain the posture. An extensor plantar in the Babinski's response and constructional apraxia are some of the vague physical examination finding.

The mainstay of treatment is treating the cause or the precipitating factor. Spontaneous Bacterial Peritonitis is considered to be one of the precipitating feature of hepatic encephalopathy along with other infections like urinary tract infection and pneumonia. Low protein was considered to be part of treatment. But that idea was not that deep rooted. As per new guidelines plant or dairy proteins are considered for the disease as for their favourable protein – calorie ratio. Non absorbable disaccharides like lactulose or lactitol improves the condition as they help in reducing the pH of the stools along with induction of catharsis. In unconscious patients, lactulose can be given as enema to avoid aspiration pneumonia.

Antibiotics also play a pivotal role in the treatment of hepatic encephalopathy . In the initial years Neomycin 1 to 3 g per day was considered but the efficacy of the regimen was questionable and the ototoxicity and nephrotoxicity was un wanted sidelines of the treatment with neomycin . Later on US FDA approved a drug named Rifaximin .

Being a locally acting drug , it sterilizes the gut and keeps a check on the overgrowth of the microbes in the gut . The dosage is 400 mg thrice daily.

Newer therapeutic modality is usage of Acarbose. It is an α- glucosidase inhibitor which inhibit the absorption of carbohydrates in the intestines and it delivers enhanced load of carbohydrate to the colon. This increases the saccharolytic to proteolytic flora which reduces the level of ammonia.

Clinically it can staged as per the West Haven classification.

GRADE	INTELLECTUAL FUNCTION	NEUROMUSCULAR FUNCTION
0	NORMAL	NORMAL
1	Personality change , attention deficit	Tremor, in coordination
2	Change in sleep- wake pattern	Asterixis, ataxic gait
3	Altered level of consciousness, confusion	Muscular rigidity, nystagmus, clonus
4	Stupor and coma	Oculocephalic reflex, unresponsiveness to noxious stimuli .

Table 1. West Haven Classification for Hepatic Encephalopathy .

Other supportive measures must also be considered while treating hepatic encephalopathy . Simple measures like maintaining oral hygiene , change of position to avoid bed sores, proper feeding technique to avoid aspiration . Some times , the zest to treat the hepatic encephalopathy might make the physician to underlook the other symptoms and the patient might succumb to death .

Some studies even states that the usage of L-ornithine L-aspartate can also be used as a treatment for hepatic encephalopathy . The amino acid enhances the utilization of ammonia within the muscles and thereby reduces the arterial ammonia level . The dosage is 20 g as infusion every 12 hours is given till the mentation is improved .

Thiamine deficiency seen as a complication of chronic alcoholism can aggravate the altered mental status . So prompt parenteral supplementation of thiamine (100mg) i.v is continued till the patient gains consciousness .

ASCITES IN CIRRHOSIS LIVER

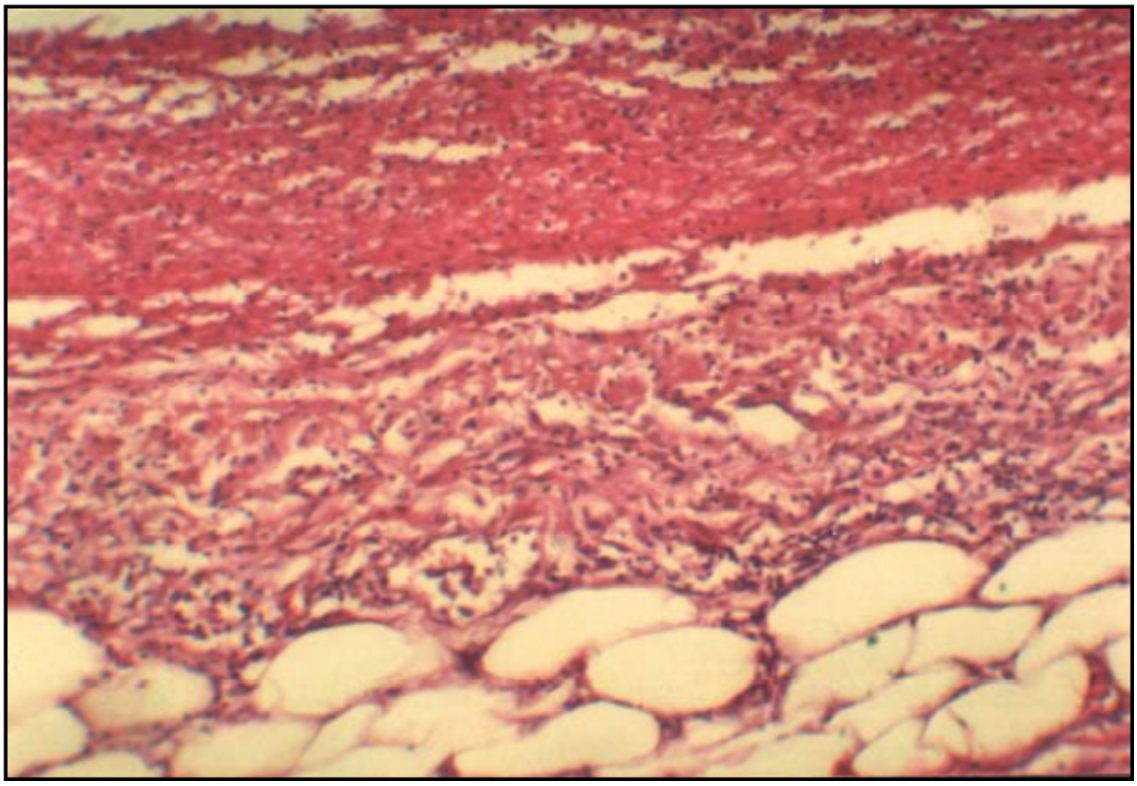


Figure 2. Histopathology of cirrhosis of liver

The term ascites refers to detectable and pathologic collection of fluid in the peritoneal cavity . Chronic liver disease with portal hypertension is the most common cause for ascites .The Peripheral Arterial Vasodilation Hypothesis is the most widely accepted explanation for ascites development and renal dysfunction in cirrhosis,as fits hemodynamic data better than the prior Underfill or Backward Theory and Overflow Theory .

Ascites is the most common complication of cirrhosis that leads to hospital admission. Within 10 years of diagnosis of compensated cirrhosis, ~50% will develop ascites. After ascites develops, 15% of patients die within 1 year, 44% die within 5 years.

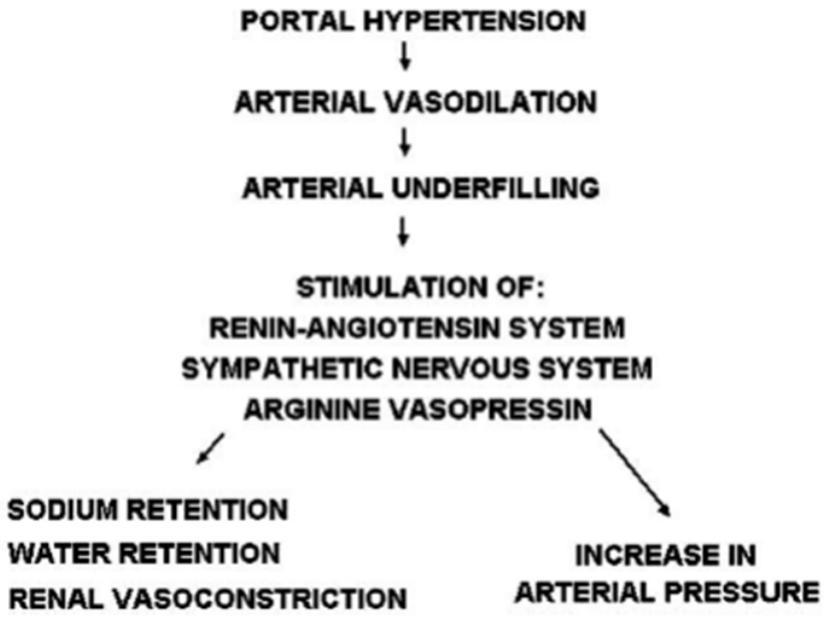


Figure 3. Pathophysiology of Ascites

As the portal hypertension increases due to progressing cirrhosis, splanchnic vasodilation occurs which plays a key role in the pathophysiology of ascites formation . Moreover endotoxemia that causes accumulation of nitric oxide and prostaglandins also adds on to the insult. This endotoxins get accumulated in the blood due to the portosystemic shunting and decreased reticuloendothelial function.

Due to the depletion of the central arterial pressure , the counter measures will be activated in the form of RAAS activity , increased sympathetic activity and ADH release is also enhanced . Ascites forms as leakage of fluid from splanchnic vessels overcomes reabsorption by lymphatics due to worsening splanchnic capillary permeability, declining oncotic pressure and increasing hydraulic pressure gradients across the splanchnic circulation.

Clinically, fluid accumulation in the peritoneal cavity will be evident to the patient when it has a volume of about 1 litre. Subtle amount of fluid in the peritoneum i.e about 250 ml can be found out by the puddle sign or even by radiological imaging. Dilated veins as shown below can be evident in most individuals. It is more evident in fair complexion individuals.

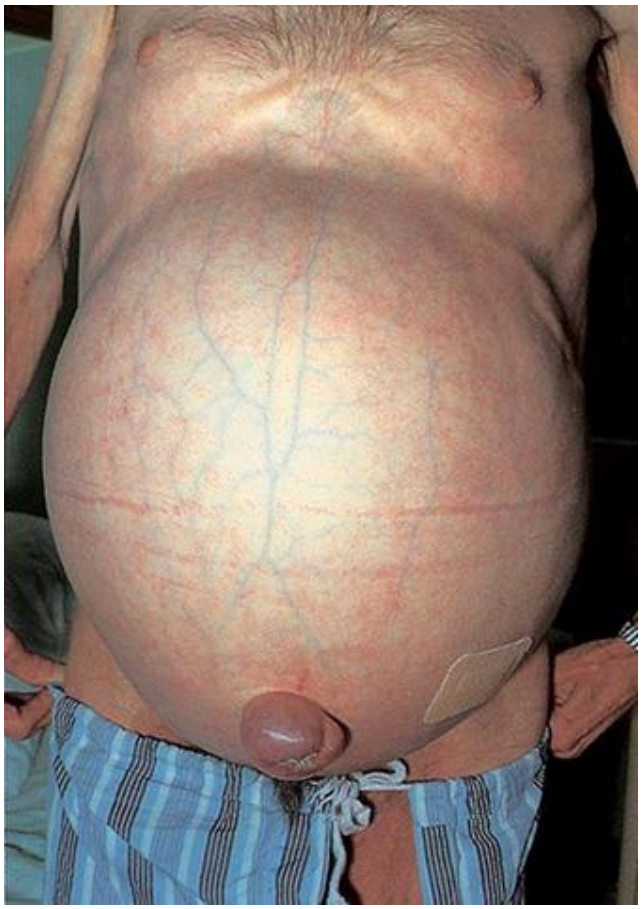


Figure 4 . Picture of patient having Ascites with umbilical hernia

In patients with ascites , renal secretion of prostaglandins particularly PGE_2 initially helps to maintain the glomerular filtration but as the PGE_2 production comes down , the glomerular filtration rate which leads to renal function detiorates . Other factors which contributes to ascites formation in cirrhosis are decreased oncotic pressure and an increased production of hepatic lymph due to post sinusoidal obstruction . Rarely even pancreatitis leading to pancreatic pseudocyst can also cause ascites . In peritoneal carcinomatosis ,

the proteinaceous leakage of fluid into the peritoneal cavity causes the exudative fluid in the peritoneum . In infection, the mechanism is similar .

Abdominal paracentesis along with careful analysis of the fluid in various aspects like biochemical, cell count and culture sensitivity is the most important procedure . A rare complication of paraentesis is abdominal wall hematoma.

The gross appearance of the ascitic fluid may be helpful in determining the pathological process . If the ascites is due to portal hypertension, the fluid is clear and straw colored , turbid ascites indicates infection and milky ascites gives a clue towards chylous ascites . Blood stained fluid indicates malignancy, tuberculosis . Brown fluid indicates the presence of bile.

The total protein concentration is also taken into account to differentiate between transudate and exudate. Low protein i.e less than 2.5 g /dl is taken as transudate whereas a higher protein of more than 2.5g /dl is considered to be an exudate. Portal hypertension or hypoalbuminemia mainly leads to transudate. Malignancy, tuberculosis and pancreatitis causes exudative ascites.

The Serum Ascites Albumin Gradient (SAAG) is another calculation and is considered to be superior to the total protein level in estimating or rather pin pointing the differential diagnosis .It is calculated by substracting the ascitic fluid albumin from the serum albumin. A value of more than 1.1 g/dl provides indicates portal hypertension. Less than 1.1 g/dl indicates exudate.

The cell count is the most important test to be performed as it gives immediate information about infection. Neutrophil equates to bacterial infection whereas lymphocyte predominance will point towards tuberculosis. Malignant cells indicates malignancy.

Culture study also helps to clinch the diagnosis of SBP. Further on glucose level also gives a clue. A low glucose level must make the clinician think in terms of either malignancy or severe secondary infection.

At present Polymorphonuclear (PMN) count is routinely done by the traditional hemtological method with a light microscope . 10 ml of the ascitic fluid taken in EDTA tube is centrifuged at 1500r / min and the supernatant is mixed with Turk's fluid and the counting chamber is filled . But the process is rather time consuming. The urinary reagent strip easily recognises leucocytes by detection of esterase activity. Another method is the estimation of lactoferrin, a protein released by PMN on activation in the presence of body fluids. This method showed a sensitivity of 95% and specificity of 97%. But the drawback of this test is the unavailability of the test always.

To date, automated counting is the best method in counting of the PMN as they provide accurate reading of the differential count .

Ascites can lead to various complications . Due to the accumulation of fluid patient will have gastrointestinal disturbances like early satiety, bloating and dyspeptic features . Sponatenous Bacterial peritonitis or peritonitis secondary to any other cause can be a life threatening complication as the

mortality is very high. Due to volume loss into the third space severe hypotension can occur and protein exudation can lead to hypoalbuminemia. Massive ascites can also cause respiratory insult as it pushes the diaphragm which on long standing period can lead to respiratory failure . Due to the hypoproteinemia and the decrease in oncotic pressure , there is also accumulation of the fluid in the other spaces like the pleural space and the pericardial space . Paralytic ileus due to electrolyte imbalance and associated pancreatitis is also seen in a few patients. Long standing untreated ascites can also cause surgical complication like umbilical hernia which can lead to obstructive hernia and spontaneously rupture and cause infection .

Cosmetic complication like the unlikely site of the distended abdomen can also lead to depression in some patients .

Local effects like excoriation of skin due to chronic friction and later on secondary infection can also be seen .

Refractory Ascites

It is a condition where a salt free diet and the maximum therapeutic dose of diuretics cannot resolve the ascites .Even the excessive use of NSAIDs can also lead to change of diuretic sensitive ascites to resistant one .Treatment includes

1. Serial paracentesis – It must be done every 2 weeks . In cases where the Na excretion via urine is very minimal, this modality has improved the burden of ascites . But while doing large paracentesis i.e more than 5 litres , it is always advisable to give albumin infusion (6 to 8 g) for every litre of ascites fluid taken .

2. As the mortality is very high at a rate of 21 % in the next 6 months , Liver transplantation must also be kept in mind

3. TIPS - Five randomized controlled trials have shown improved control of ascites with TIPS compared to serial LVP's in patients with refractory ascites (62% vs. 24%). However, there was also more cases of encephalopathy with TIPS (39% vs 23%). The incidence of new or worsening HE was 20-31%.

4. Peritoneovenous shunt . - Peritoneovenous shunt has high complication rates and so is only used on rare occasions in patients who are not candidates for paracentesis, transplant or TIPS.

Now there is a condition called as hepatic hydrothorax in cirrhosis . It is most commonly seen on the right side, but can also be seen on the left side and bilaterally. It is considered to be caused due to the large pores over the right side of diaphragm. In about 20% of cases there is no ascites. But even if the diaphragm is intact in several cases, it is also found to be present over the left side and bilaterally which is attributed to the attachment of the bare area of liver with the pleural cavity.

The mainstay in the treatment of hepatic hydrothorax is similar to that of treating the ascites. This includes low salt and diuretics usage. In about 20% of patient, the hydrothorax is resistant to treatment , which is referred to as refractory hydrothorax similar to 10 % refractory ascites .

The other treatment modalities are

1. Thoracentesis and Paracentesis – it can be used to relieve dyspnea , respiratory distress or hypoxia

2. Percutaneous Drain - Tube insertion must be avoided because of multiple complication like pneumothorax , hemothorax , empyema and hepatorenal syndrome . It has been noted that chest tube insertion has caused complication in 80 % of patients and 33 % patients died .

3. TIPS – The success rate of rate 70 to 80 % . But there are some contraindications for the procedure like age more 70 years , significant

hepatic encephalopathy , large portal vein thrombosis , right – sided heart failure and elevated pulmonary arterial pressures

4. VATS - Video Assisted Thoracoscopy – It helps in the detection of defects in the diaphragm . It is superior to open thoracotomy and has less complication .

Another treatment modality is pleurodesis that consist of ablation of the space between the parietal and visceral pleura with a sclerosing therapy .

Figure 5 . Chest X ray showing Right Pleural effusion

PATHOPHYSIOLOGY OF SBP

Spontaneous bacterial peritonitis as the name indicates is the infection of the ascitic fliud in the absence of any source of infection. The passage of bacteria into the mesenteric lymph nodes and then to the blood stream and the other extra intestinal sites is considered to be the most accepted hypothesis [9]. Moreover, in cirrhotic patients the vascular stasis due to portal hypertension and impairment of local defence mechanism leads to the overgrowth of micro organism within the gut . This also adds onto the infection progression. Hypochlorhydria commonly seen in cirrhotic patients can also cause bacterial over growth .

Other sites from which the bacterial seeding can occur are pneumococcal sepsis, cellulitis, urinary tract and dental infections.The complications seen in SBP like renal failure and shock that leads to adverse prognosis are attributed to the high-levels of TNF-α (tumor necrosis factor-α), IL-6 (interleukin-6) and IL-1 (interleukin-1) in-patients with cirrhosis that causes over-activation of the sepsis syndrome pathways[10]. Bacterial translocation by definition means the movement or rather penetration of the microbes through the mucosa into the lamina propria which later on migrate into the mysentric lymph node and from there into the fluid . Abnormality in IgA production has also seen to cause immunosuppression in cirrhotic patients .

The decreased protein level in the ascitic fluid is considered a risk factor for SBP as the opsonin level is also decreased which play a key role in the

defence mechanism. In the initial phase , the bacteria accumulates in the fluid and it can lead to bacterascites . Mostly it is Monomicrobial Nonneutrocytic Bacterascites (MNB) unless the intergrity of the mucosa is lost which can cause Polymicrobial invasion. Later on as the opsonins and macrophages fail as in the case of chronic liver disease , the ultimate defence mechanism that is recruitment of neutrophils occur which leads to neutrocytic ascites . But as the function of the neutrophils are lost in cirrhosis liver, it culminates in SBP . So , the differentiation of the diagnosis into bacterascites , CNNA, MNB and neutocytic ascites eventually to SBP all depends on where the disease process stops and the fluid is taken up for diagnosis .

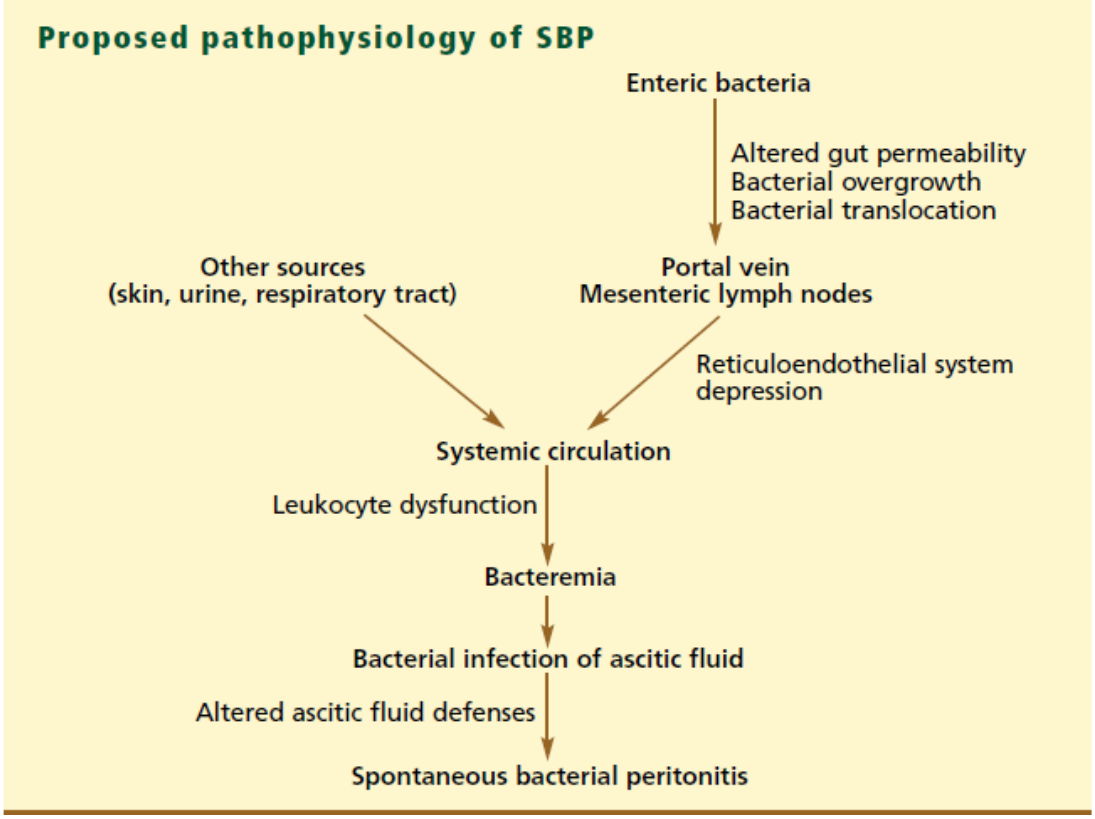


Figure 6 . Pathophysiology of Spontaneous Bacterial Peritonitis

MICROBIOLOGY OF SBP

The microbe isolated from the ascitic fluid is usually that of normal intestinal flora most commonly being E.coli. Majority of the infection is caused by Gram negative organism with mostly by E. coli closely followed by Klebsiella . About 25 % of the organism are gram positive with Streptococcal infection been the most common . Rarely anaerobic organism can also be the etiological agent. But if a mixed organism is detected from the ascitic fluid , a secondary cause for peritonitis must be thought of .

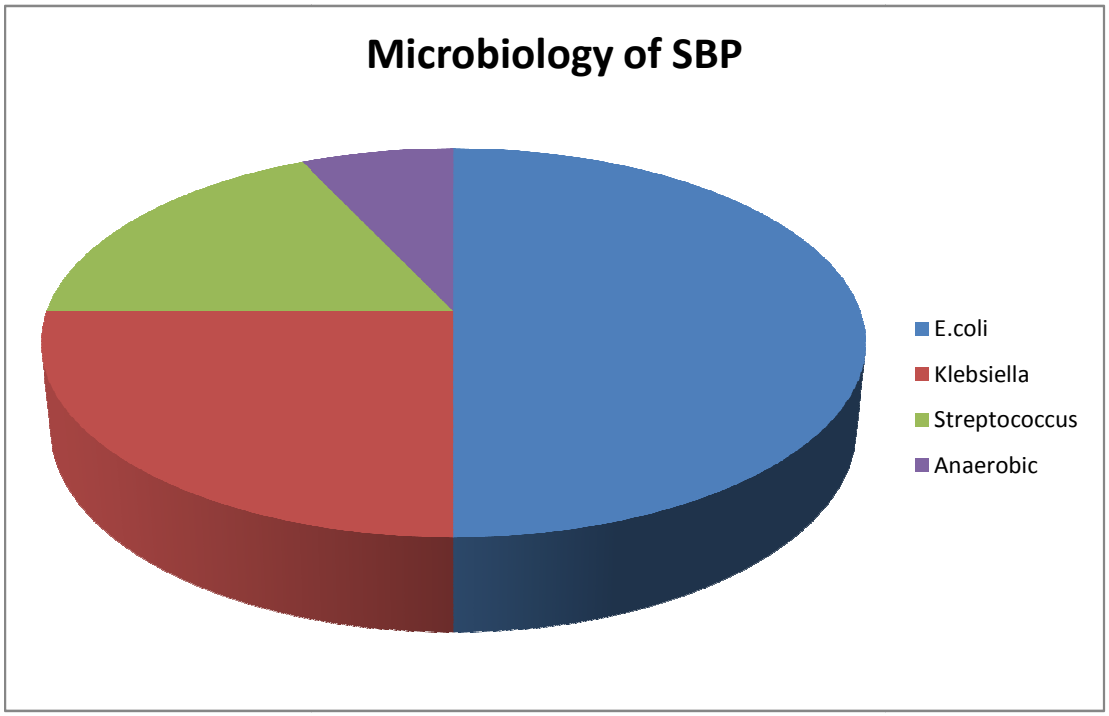


Figure 7. Microbial Spectrum in SBP

CLINICAL PRESENTATION

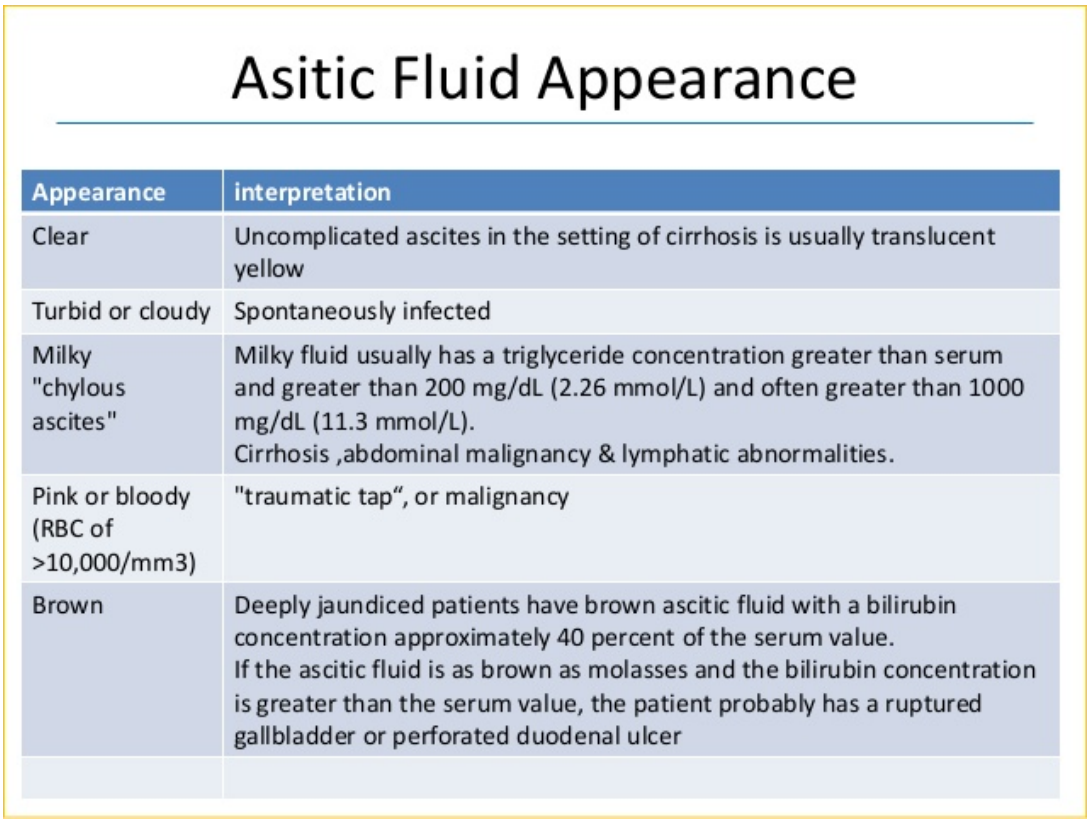
In the initial stages of SBP , a patient may not have any symptom which highlights the fact that early stages of SBP are less aggressive and associated with better prognosis .Fever is the most common clinical symptom as it is evident in almost 60% of patients with SBP .The other features include abdominal pain with altered sensorium and hypotension . Still some patients will present with diarrhea and paralytic ileus . However, signs of sepsis in patients with SBP may be masked because patients with cirrhosis have characteristics which make recognition of sepsis difficult namely, reduced polymorphonuclearleukocyte (PMN) count due to hypersplenism, elevated base line heart rate due to the hyperdynamic circulation, baseline hyperventilation due to hepatic encephalopathy, and blunted elevation of body temperature .

INVESTIGATIONS

Prior to the analysis of the ascitic fluid which clinches the diagnosis , a complete blood count will show an increased polymorphonuclear cells with thrombocytopenia . The renal function test is also deranged in most cases and some cases can also have an unexplained metabolic acidosis .

Diagnostic paracentesis with analysis of the ascitic fluid is the only method to confirm Spontaneous Bacterial Peritonitis . It has to be done in any new onset ascites including congestive cardiac failure and Budd Chiari syndrome. It must also be done in any cirrhotic patients with unexplained

encephalopathy and renal failure . Moreover a sudden deterioration of general condition of a patient must also prompt us in doing a diagnostic paracentesis [11]



Asitic Fluid Appearance

Appearance	interpretation
Clear	Uncomplicated ascites in the setting of cirrhosis is usually translucent yellow
Turbid or cloudy	Spontaneously infected
Milky "chylous ascites"	Milky fluid usually has a triglyceride concentration greater than serum and greater than 200 mg/dL (2.26 mmol/L) and often greater than 1000 mg/dL (11.3 mmol/L). Cirrhosis ,abdominal malignancy & lymphatic abnormalities.
Pink or bloody (RBC of >10,000/mm3)	"traumatic tap", or malignancy
Brown	Deeply jaundiced patients have brown ascitic fluid with a bilirubin concentration approximately 40 percent of the serum value. If the ascitic fluid is as brown as molasses and the bilirubin concentration is greater than the serum value, the patient probably has a ruptured gallbladder or perforated duodenal ulcer

Figure 8 . Types of Ascites according to appearance

The main parameters to be taken into consideration are

1. Cell count – neutrophil count
2. Culture sensitivity

As mentioned above a total count of neutrophil more than 250 cells/ cu.mm warrants the start of antibiotic therapy . Bed side inoculation of the ascitic fluid has increased the detection of the culprit organism [12].An optimal

10 ml of fluid inoculation gives a good result . The sensitivity of the culture analysis has shown drastic reduction in linear proportion to the amount of sample taken .

Other parameters that are taken into consideration is the Lactate Dehydrogenase (LDH) level . A level of greater than 400 sigma units was considered as useful tools for determining the diagnosis .

Imaging techniques also play a key role in the investigation of ascites . It can give us a clue regarding the etiology of the ascites. Abdominal ultrasound is till date the most cost effective and best imaging technique due to the fact that it has no risk of radiation and iv contrast. CT and MRI has advanced application in narrowing down the etiology of the ascites like carcinoma , tuberculosis or pancreatitis .

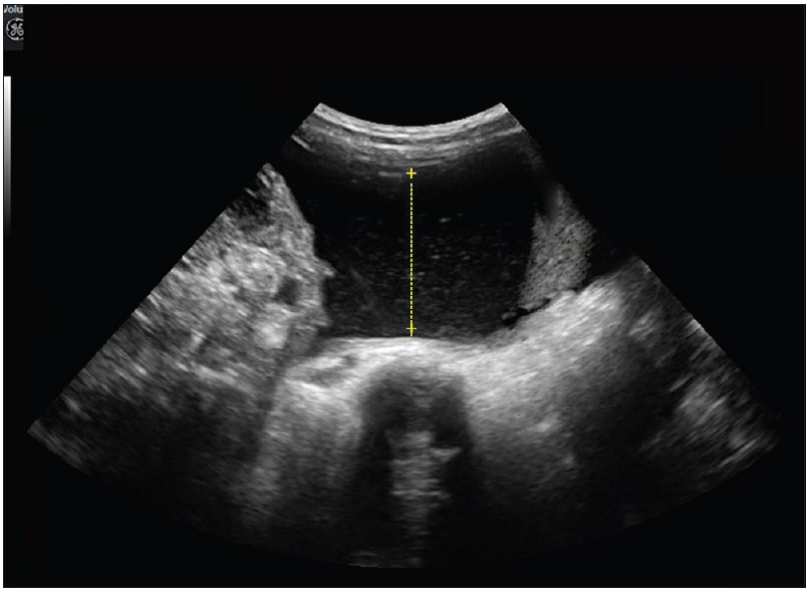


Figure 9.An ultrasound picture showing ascites .

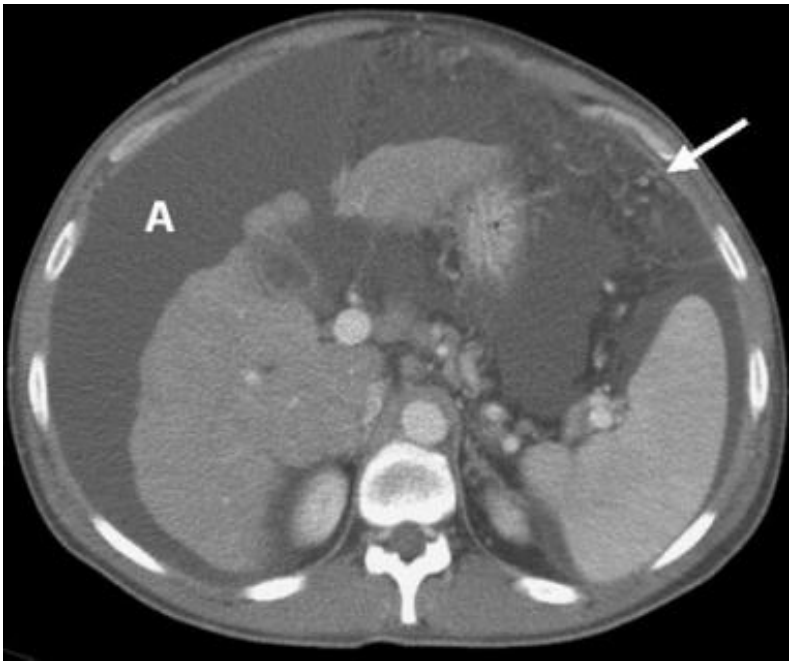


Figure 10. CT abdomen showing Ascites

TREATMENT

A prompt use of antibiotics in a case of SBP has shown improvement in the outcome of patients but still as per literature the mortality is still high as of 10 to 30 % . As the most common organisms causing SBP are Enterobacteriaceae and non-enterococcal streptococci, the antibiotic used must also be chosen that cover the same . In the initial era , an aminoglycoside along with ampicillin. Later on studies showed that cefotaxime shows superior response to SBP than the combination [13]. Moreover the combination of tobramycin along with ampicillin has seen to end in renal failure in various studies . Although the suggested duration of treatment is 14 days of intravenous cefotaxime , a study stated no difference in the recurrence or treatment of

infection in a 5 day and 10 day treatment regimen . Another study revealed that iv cefotaxime therapy is as effective as oral ofloxacin [14].

Assessing the outcome of the treatment is as important as starting the treatment. A repeat fluid analysis has to be sent after 2 days of starting treatment. A reduction of polymorphonuclear cells by 25 % is considered as a failure which should prompt the physician to re assess the antibiotic regimen.

In addition to antibiotics, albumin administration is also considered to be effective and the survival rate is high in various randomized trials.

Its clearly noted that administration of simultaneous albumin along with antibiotics has reduced the incidence of renal failure and in hospital mortality [15].

The standard treatment regimen for Spontaneous Bacterial Peritonitis

DRUG	DOSE	ROUTE	DURATION
Cefotaxime	2g every 8 hrs	I.V	5 days
Ceftriaxone	2g every 12 hrs	I.V	5 days
Amoxicillin plus clavulanic acid	1g/0.2g every 6-8 hrs	Oral	2 days
Ofloxacin	400mg every 12 hrs	Oral	8 days

Table 2 .Treatment for SBP

As the golden rule states, prevention is always better than cure. So as the mortality and the disease outcome of SBP is still high, a measure to prevent it is always wise . Choosing of the antibiotics wisely is very important. Use of antibiotics targeted against anaerobes is not prudent as it will cause bacterial over colonization in the gut .Moreover unwisely antibiotic choice will cause the emergence of resistant microbes [16].

Yet another study states that a low protein level in the ascitic fluid has shown an increased risk of SBP [17]. But later on it was found that a level of less than 1g/dl only had the predictive value of occurrence of SBP. The opsonic activity i.e the endogenous antimicrobial activity of the ascitic fluid has strong co relation with the protein levels of the fluid. This statement holds strong as the occurrence of SBP is seen to be high in low protein ascitic fluid [18].

The prophylactic therapy for SBP in cirrhotic patients are advised for those with Upper Gastrointestinal Bleed, prior history of SBP and a low ascitic albumin level. Gastrointestinal bleed causes hypotension which per say leads to shock. As the intestinal perfusion is decreased, the mucosal permeability for microbes is increased . this leads to translocation of intestinal microbes into the mysentric lymph nodes and from there to the peritoneal cavity[19,20] .So , in conclusion the incidence of SBP following upper GI bleed is high in case of associated shock and rather than hemodynamically stable patients [21]. But , UGI bleed per se is a risk due to the loss of defense mechanism attributed to the local mucosal erosion and following endoscopic intervention . So a

prophylactic antibiotic course lasting for 7 days is advised for all patients admitted with UGI bleed [22].

HEPATORENAL SYNDROME

One of the dreaded complication of SBP is Hepato Renal Syndrome. It is characterised by functional renal dysfunction that is exclusively seen in patients with ascites. It is seen as the sequalae of circulatory failure in chronic liver disease . There are 2 types .

The main pathophysiology of HRS is the raised arterial resistance that affects the cortex of kidney that leads to hypotension. Due to the adiuretin-vasopressin activity, final urine is produced through an essentially zero hyperosmolar natriuresis, and its quantity ranges between oliguric and anuric values.

The predisposing factors that goes in favour of Hepato Renal Syndrome are ascitic patients with a small liver , esophageal varices and an uncontrolled diet .Dilutional hyponatremia , hypotension and tachycardia are warning signs in hepatorenal syndrome .

Type 1 - rapidly progressive, where the serum creatinine doubles in 2 wk and values of approximately 350 μmol/L (2.5 mg/dL) are usually achieved. This type accompanies clinically more serious conditions and it is typically unstable. Its main clinical feature is acute renal failure. Type 2 - slowly progressive, this state was described later and, despite the otherwise typical

signs of hepatorenal failure, it is quite stable. Serum creatinine rises slowly or not at all and it usually does not exceed 180 μmol/L (1.3 mg/dL). The clinical record is dominated by refractory ascites and relatively stable liver function.

New diagnostic criteria of hepatorenal syndrome
Cirrhosis with ascites
Serum creatinine > 133 μmol/L (1.5 mg/dL)
No sustained improvement of serum creatinine (decrease to a level of 133 μmol/L or less) after at least 2 d of diuretic withdrawal and volume expansion with albumin; the recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/d
Absence of shock
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal disease as indicated by proteinuria > 500 mg/d microhematuria (> 50 red blood cells per high-power field) and/or abnormal renal ultrasonography

Figure 11. Diagnostic criteria for Hepatorenal Syndrome

The criteria given above was brought about by the International Ascites Club .

The mean survival rate of type 1 HRS is 2 weeks whereas that of type 2 is 4 to 6 months .[23]

Treatment is multifactorial . The root cause can be SBP , esophageal variceal bleed , usage of NSAIDs , antirheumatic drugs ,elimination of nephrotoxic and diuretics . Supplementation with albumin as a plasma expander also gives a better response as it is considered to be the best expander with long lasting impact.

Measures must also be taken to improve the hypovolemia . Retrospective studies have proven that the use of midodrine (α- agonist vasoconstrictor) along with nor adrenaline and octreotide associated with administration of albumin has shown to improve the renal function by 40 to 60 % in HRS type 1. Dopamine was initially used but the effectiveness was questionable with or without combination with ornipressin .

Currently the drug of choice is terlipressin .The treatment is initially started with 1 mg every 6^{th} hourly . A serial creatinine value must be checked for . If it is on an increasing trend it must be increased to a maximum dose of 3 mg 6^{th} hourly . TIPS has also shown to improve the pathophysiology as it leads to increased urinary excretion of sodium along with increased urine volume and plasma clearance .

Now it is prudent to give a prophylactic or rather a pre treatment therapy of fresh frozen plasma prior to paracentesis as the patient will always have bleeding tendency due to the deficiency of clotting factors . A very rare complication of abdominal paracentesis is abdominal wall hematoma formation . Giving a prior dose along with choosing an appropriate site for the paracentesis will reduce this avoidable risk drastically . The site to be normally taken is a median site just below the umbilicus . The same level in the flanks can also be taken .

As mentioned in the earlier part , the incidence of asymptomatic SBP is very low. In the past, several studies were done regarding studying the incidence. But there were various drawbacks and difficulties faced by the investigators. Some of them were that patients were difficult to be categorised and taken up for the study as there were no specific criteria or guidelines to label them as Asymptomatic SBP. Later on in 1998 the American Association for the Study of Liver Disease (AASLD) published guidelines for the initial ascitic fluid analysis in outpatients with cirrhosis [24]. It states that a second paracentesis is warranted if the initial paracentesis showed a neutrophil count of 250 cells / mm^3 . Another study revealed that most of the patients coming as out patients had no growth in the ascitic fluid during paracentesis [25].

In a study conducted by Evans et al in the Mayo clinic division of Gastroenterology and Hepatology in 1994 revealed various in sights into asymptomatic spontaneous bacterial peritonitis. In that study , the investigator made sure that the patients selected had no symptoms suggestive of Spontaneous Bacterial Peritonitis. This included exclusion of fever, gastrointestinal bleed , significant abdominal tenderness and rapid deterioration of renal function . Patients who had prior history of SBP and those on antibiotic prophylaxis were also extempted. The study was conducted and the outcomes were recorded. Out of the 427 patients studied 15 of them were found to have SBP who fulfilled all the criteria for the same .

Among the patients , the spectrum of the microbes involved were as follows

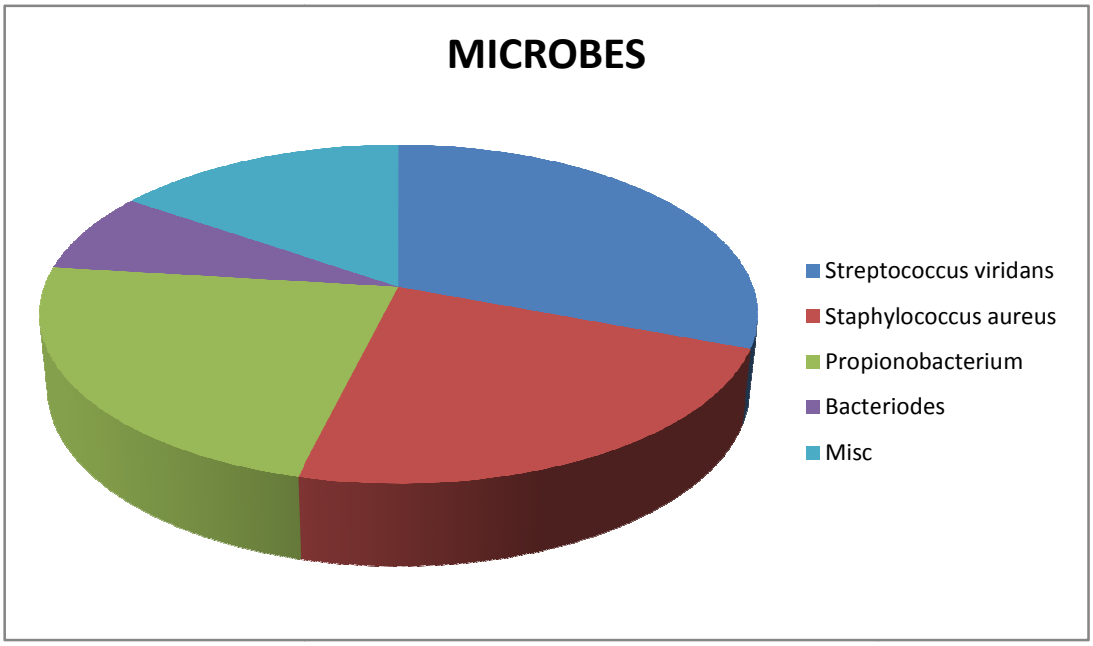


Figure 12. Microbial spectrum

The majority of the micro organism were Gram positive organism with Streptococcus viridans being the highest in number . It was closely followed by Staphylococcus aureus. The spectrum showed that Gram positive organisms were the etiological agent in most of the cases . It was also found that the protein level was also low in patients with SBP . So the study proved that the incidence of Asymptomatic Spontaneous Bacterial Peritonitis in cirrhotic patients were low .

Another study conducted by Jean Francois Cadranel in France was a study between the incidence of SBP in out patients and inpatients undergoing therapeutic paracentesis . The result showed that the prevalence was 11.7 % in inpatients and 3.1 % in outpatients . Among the out patients ,the prevalence of symptomatic SBP was 8.3 as compared to 3.1 in asymptomatic . Like the previous study , care was taken by the investigator to avoid symptomatic patients to be included in the study .

The outcome of the study was that there was a low prevalence of asymptomatic SBP as compared to peritonitis following the paracentesis , so an unwanted paracentesis can be warranted of .

Now some light has to thrown on the Indian studies too .Various studies regarding Spontaneous Bacterial peritonitis has been conducted in various parts of the country .

A study conducted at the ***University College of Medical Sciences and Guru Teg Bahadur Hospital, Shahdara, Delhi*** had the following results . About 41 patients were taken into the study after a series of inclusion and exclusion criteria . The mean age of the patients were 44 yrs .The prevalence of the SBP in the study was 34.14 %.

Out of the 41 , 11 were found to have spontaneous bacterial peritonitis . The microbiological spectrum were similar as the western population with Gram positive cocci as the causative agent in majority of the patients . It

was closely followed by Gram negative bacilli and other miscellaneous organisms .

When prioritised as per Child Tourette Pugh Score out of the 11 patients with SBP 9 had class C and 2 had class B .It was also found that the protein level in the ascitic fluid was less than 1 gm /dl in 6 of the patients . The SAAG ratio was conclusive of Portal hypertension. They also correlated that the incidence of SBP also increased with the severity of cirrhosis by the child pugh score.

In a general survey of Spontaneous Bacterial Peritonitis, it was found that 10 to 13 % are asymptomatic [26]. It is significant as SBP is a life threatening complication and without prompt treatment the mortality rates are high. The other clinical features are fever , abdominal pain, rigors , nausea , hypothermia , diarrhea ,paralytic ileus and shock in the descending order . Another clinical correlation is that the volume of the ascitic fluid is directly proportional to the increased risk of developing SBP. Conversely , the chance of developing SBP in the the absence of ascites is also very low . As mentioned in the previous studies the Child Pugh score can also be taken as an indicator of SBP . It was found that 96% of patients with SBP had either Child-Pugh grade B or C.

Rebound tenderness considered to be present in SBP as per the old studies is not considered to be reliable as just abdominal pain is seen in most of the patients .[27]

As mentioned earlier , Hepatic encephalopathy in the scenario of SBP is very common and the subtle mental derangement is seen in about 50 % of cases . There is a steady fall in the mortality of inpatients with SBP. It is due to the prompt diagnosis and appropriate treatment. With the discovery of antibiotics and better investigation and diagnostic techniques, the patients in hospital stay has also come down.

In the western population, due to the early awareness and prompt treatment , the mortality due to SBP is kept to a check . With the advent of advanced investigation techniques, the deteriorating course of the disease has taken a new turn . In the tertiary health care centres, the outcome of patients with SBP has improved .

But as nutritional status along with environmental factors of the patient plays an important role in the pathogenesis of SBP , its mortality remains high in the third world countries . But the statistics compared to the earlier years are better .

PREVENTION

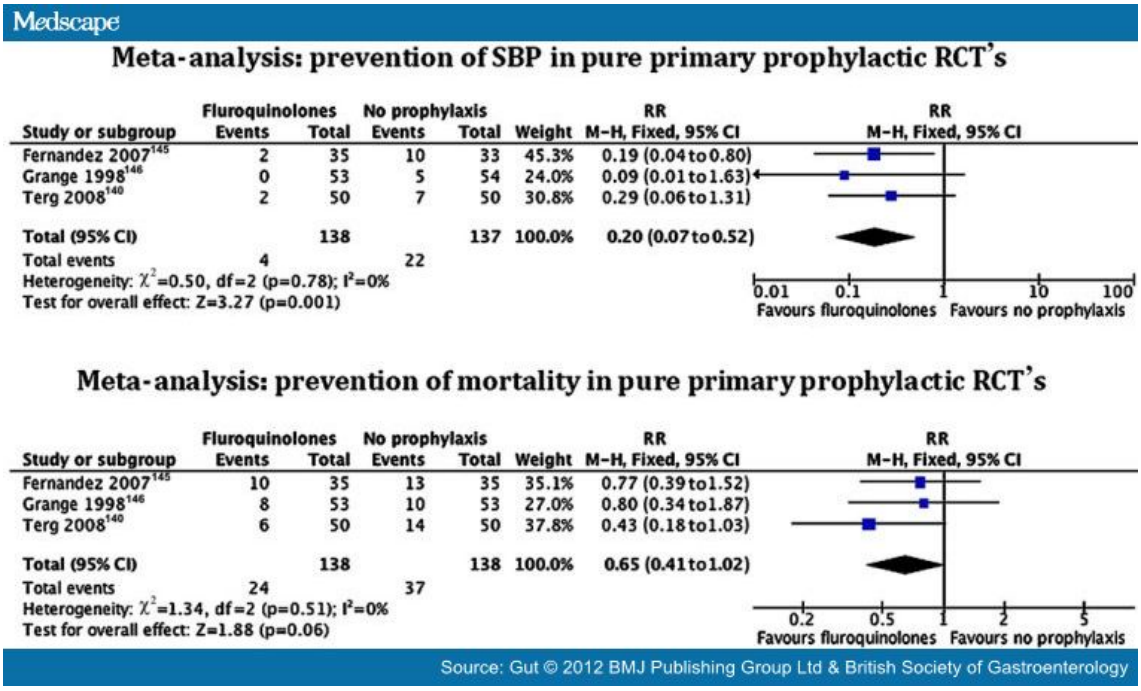


Figure 13 . Meta analysis of prevention of SBP by Prophylaxis

Prophylaxis with antibiotics plays a key role in the prevention or the second attack of SBP. The classic teaching is the usage of flouroquinolones . . In fact, survival advantage using norfloxacin as primary prophylaxis in highly selected patients is most marked during the first 3 months of treatment (94% vs 62%, p=0.003) and decreases over time.

But due to the emergence of resistance, a cycling of antibiotics i.e , a use of an alternative antibiotic is effective to fight the tide. Rifaximin is considered as an ideal drug for this. It is so because it exerts a broad spectrum of antibiotic action, it has less considerable resistance and has maximum action in the small intestine .

Still further the use of a Non Selective Beta Blocker (NNSB) along with an antibiotic is also very effective and has shown positive results in various retrospective studies. Propranolol with norfloxacin has shown publishable results. Cisapride, a 5 HT4 receptor agonist has shown to reduce Small Intestine Bacterial Overgrowth (SIBO) which again can pave the path for SBP.

Conjugated bile acids, cholylsarcosine, insulin-like growth factor and anti-tumour necrosis factor has also shown to be effective in ameliorating Peritonitis. It has effectively reduced the endotoxemia in the gut . Lactobacilli along with fibre has also reduced the mortality among several cirrhotic patients. Probiotics may even be helpful in limiting the development of bacterial resistance, and trials are ongoing to investigate their efficacy in eradicating carbapenem-resistant bacteria as well as the decolonisation of MRSA in carrier patients.

Spontaneous Bacterial Peritonitis is hence considered to be a treatable complication of cirrhosis liver if acted up on promptly .

A recent study incorporated age and sodium values to the MELD score which is at present known as the iMELD which has been proven to be a better predictor of outcome in decompensated cirrhotic patients . It is given by the formula

iMELD = MELD + (age x0.3) – (0.7x Na) + 100

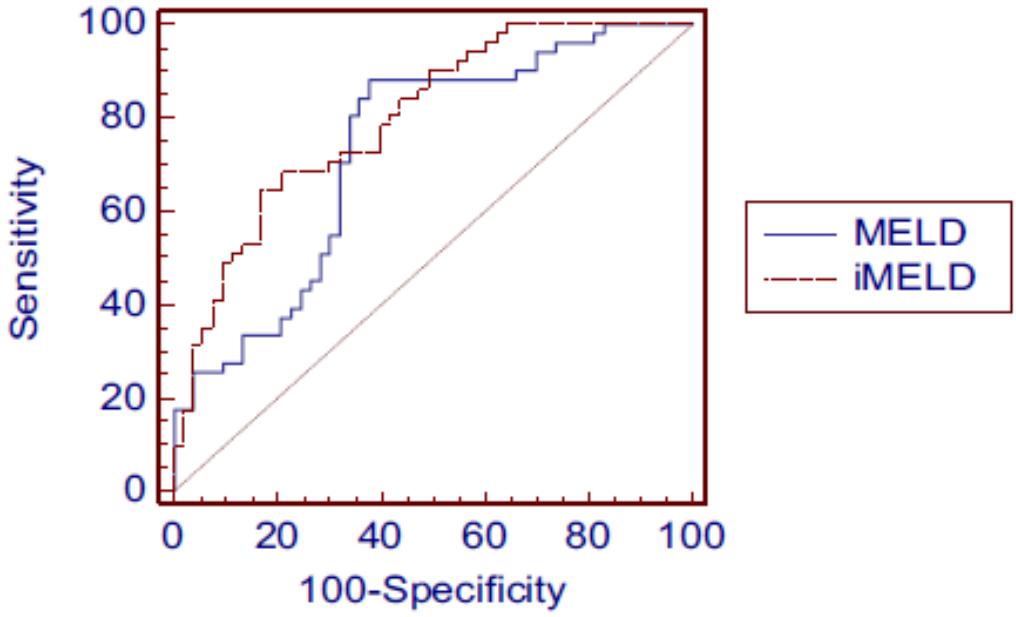


Figure 14. Sensitivity and Specificity difference with MELD and iMELD

This effective prognostic criteria has helped in further improvement of the quality of care in SBP patients and thereby reduce the mortality rate during hospital stay .

This disastrous complication hits very hard at the lower economic class . One is that the low economical class individuals are more prone to develop SBP due to the poor hygiene status. Moreover, if the mortality rate is soaring , the financial burden of the family is also high as compared to the higher economical society status . Patients must be made aware of the signs that points to the complication of cirrhosis liver. Emphasis on regular clinical follow up must enable the clinicians to reduce the burden of SBP.

MATERIAL AND METHODS

STUDY DESIGN : Observation study

INCLUSION CRITERIA

1. Patients with known history of cirrhosis presenting with Ascites

EXCLUSION CRITERIA

1. Not on prophylactic
2. No history of fever in the past two weeks
3. No features of hepatic encephalopathy
4. No features suggestive of pre existing intra abdominal infection .
5. No features suggestive of renal failure

METHODOLOGY

Patients with Ascites and those who have undergone ultrasound scan and proven cirrhosis are selected for the study. After that a fresh ultrasound is also done to rule out any active infection and other clinical conditions that can interfere with the exclusion criteria like pancreatitis. They should also fulfil the inclusion and exclusion criteria. After taking informed consent 10 ml of ascitic fluid is collected and sent for various biochemical analysis like proteins and sugar along with cell count.

The cell count is measured by Neubauer's chamber. Equal quantity of ascitic fluid and Turk's WBC solution is mixed and kept aside for 10 mins. Then the solution is put in the chamber and it is visualized under high power. 10 high power fields are observed and the count is taken. the count multiplied by 40 is taken as the count in 1 cu.mm .

Another 10 ml was taken and sent for culture and inoculated into culture tubes under aseptic precaution . Initially the fluid is made into smears and gram staining is done. Later on the fluid is inoculated into three culture media which are

1. Nutrient agar slope
2. Blood agar to
3. Mc Conkey agar

Each of the above given culture study is incubated for 24 hours at 37 □ C . After that the corresponding colonies that show the response is segregated to identify the organism.

Along with it a liver function test, serum amylase and prothrombin time is also done. To avoid person to person error the same person have to collect the ascitic fluid. It is also sent to the same lab. Soon after the procedure, a prophylactic antibiotic course is started. With the parameters, the Child's Tourette Pugh scoring is also done. After the reports come, appropriate treatment is promptly started.

SOURCE OF SUBJECTS

Patients who get admitted in the medical and gastroenterology wards for ascites

SOURCE OF DATA

Data collected by the principle investigator from the patients admitted in medical and gastroenterology ward in Coimbatore Medical College Hospital

DURATION OF STUDY

July 2014 to July 2015

OBSERVATION AND RESULTS

The study population consisted of 50 patients who had full filled the inclusion and exclusion criteria. Retrospectively, the duration of cirrhosis was also noted. After taking a fresh USG abdomen, the ascitic fluid analysis was sent as decided in the methodology.

Age and sex of the study population was as depicted below

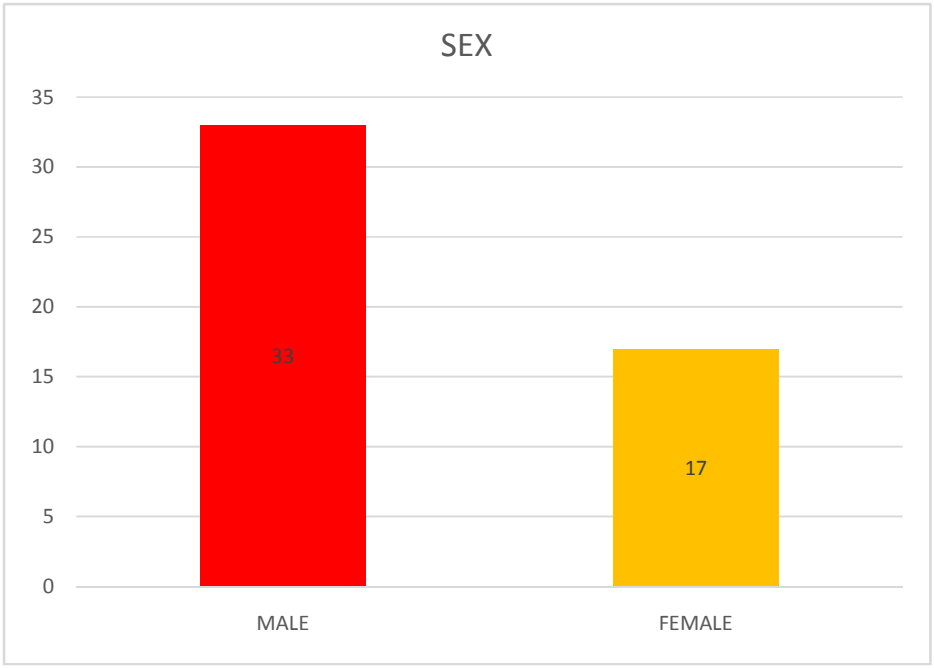


Chart 1 . Sex distribution in the study .

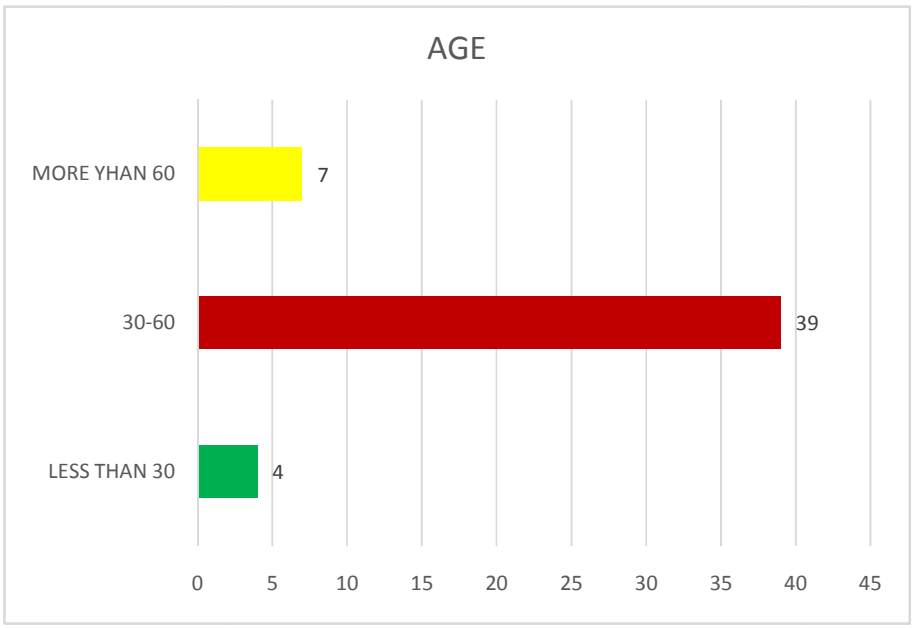


Chart 2.Age distribution in the study

Among the study members, about 40 % were non alcoholics and 60 % were alcoholics

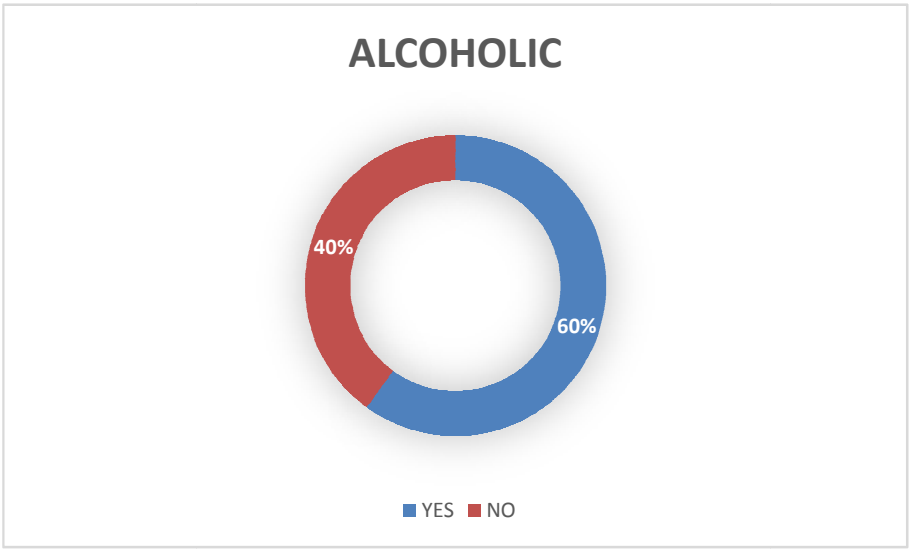


Chart 3. Percentage of Alcoholics in the study

60% of my study population had cirrhosis for more than 5 years and 40 % had cirrhosis for less than 5 years

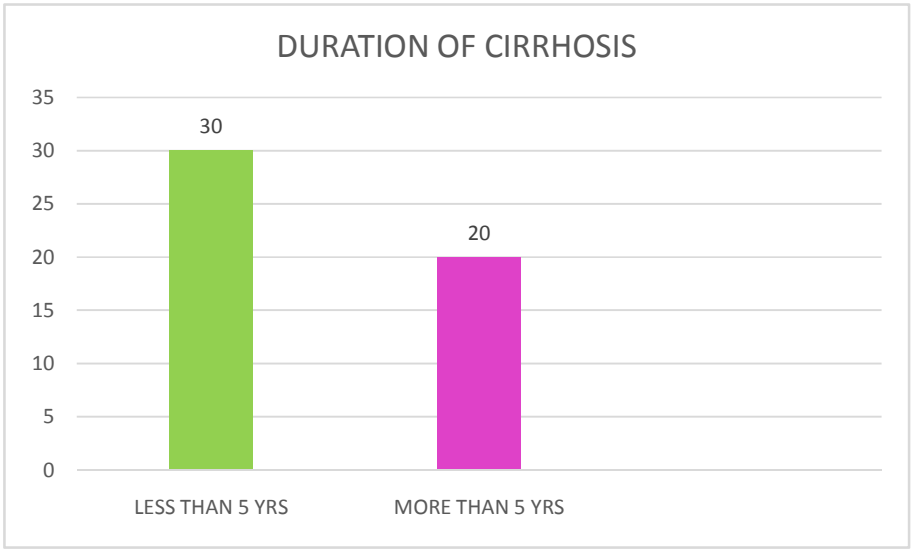


Chart 4 . Duration of cirrhosis in the subjects

The ascitic fluid analysis was like only around 5 of the population had cells more than 250 / cu.mm

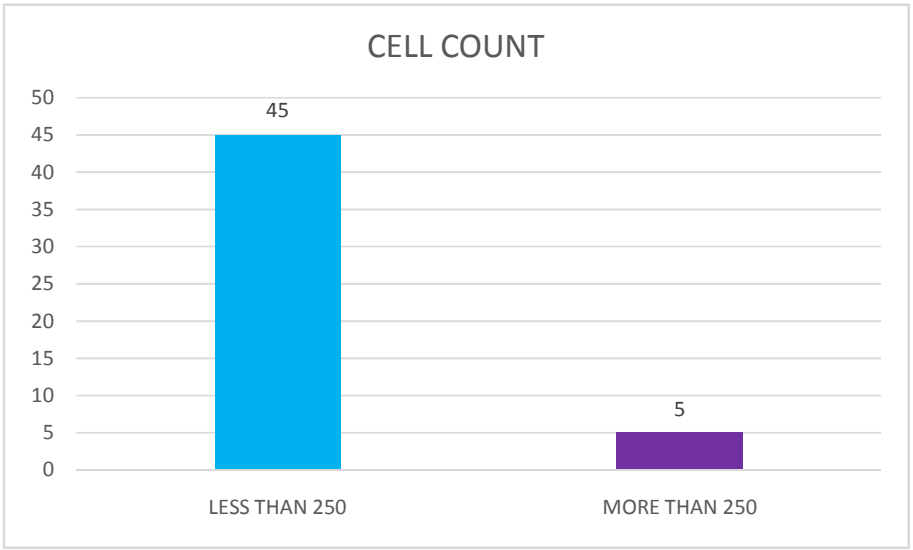


Chart 5 .Cell count distribution in SBP

Culture study trend was like around 12 % of the patients were culture positive. Among the organisms studied, the majority was E. coli and the others were Streptococcus and Klebsiella .

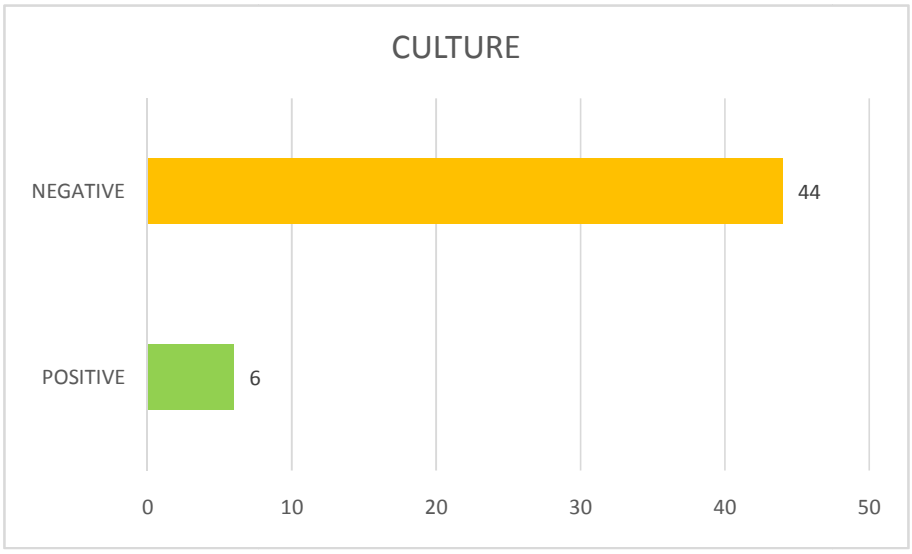


Chart 6. Culture report of the study

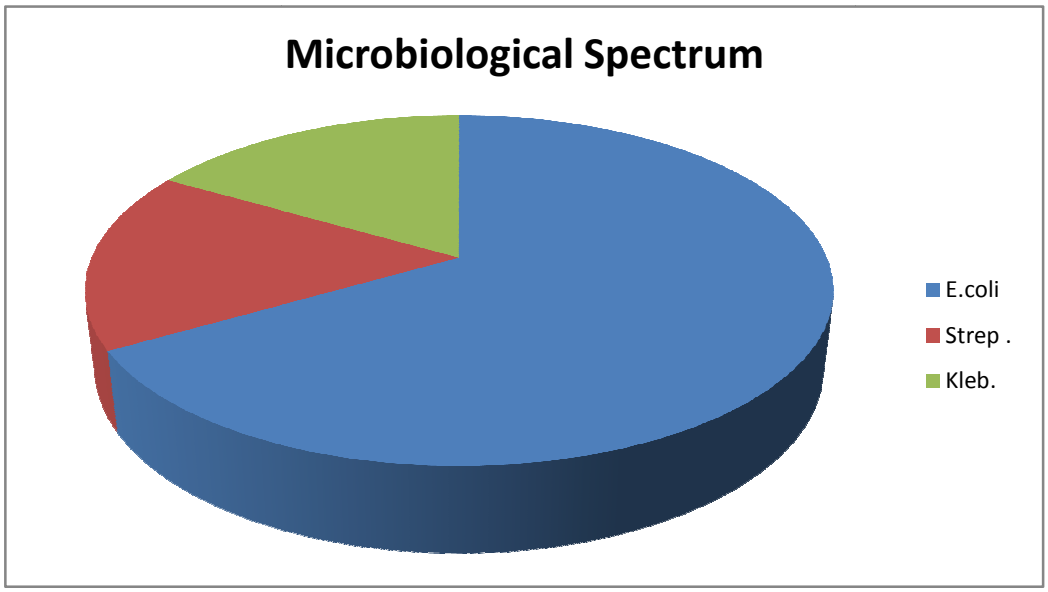


Figure 15. Microbial spectrum in the study

Among the 50 patients, only 8 of the patients were found to have SBP. It was decided either with a total cell count of more than 250 / cu.mm or with a culture positive study. So the calculated prevalence was **16 %**

The Child Pugh scoring was calculated as per the criteria mentioned earlier and the majority came under Class B , followed by Class A and the least by Class C .

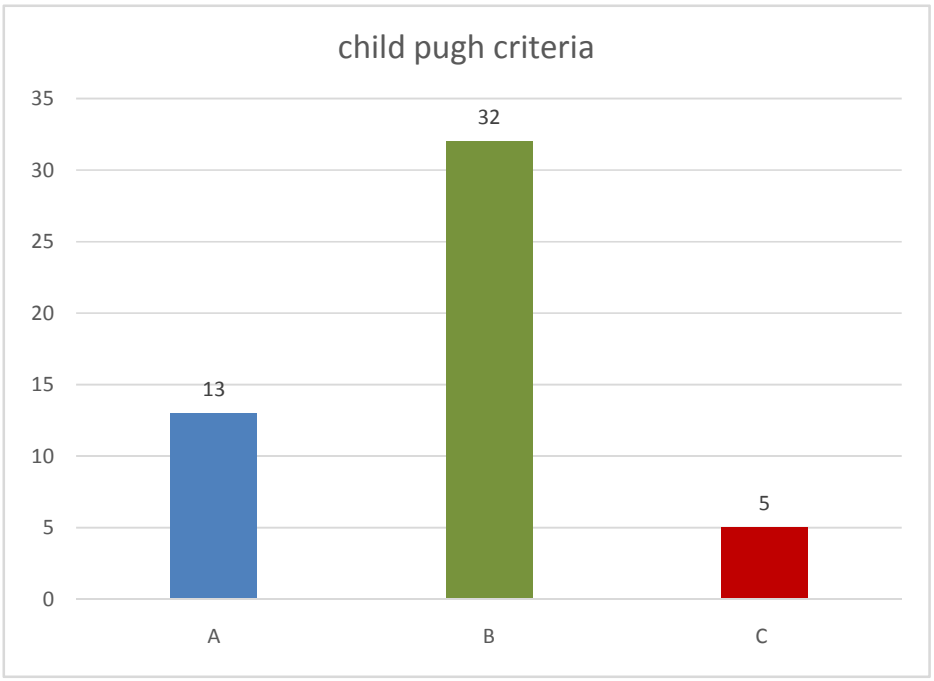


Chart 7. Distribution of Child Pugh's Classification

The ascitic fluid protein level was correlated with the incidence of SBP and it was also found significant at $p < 0.05$

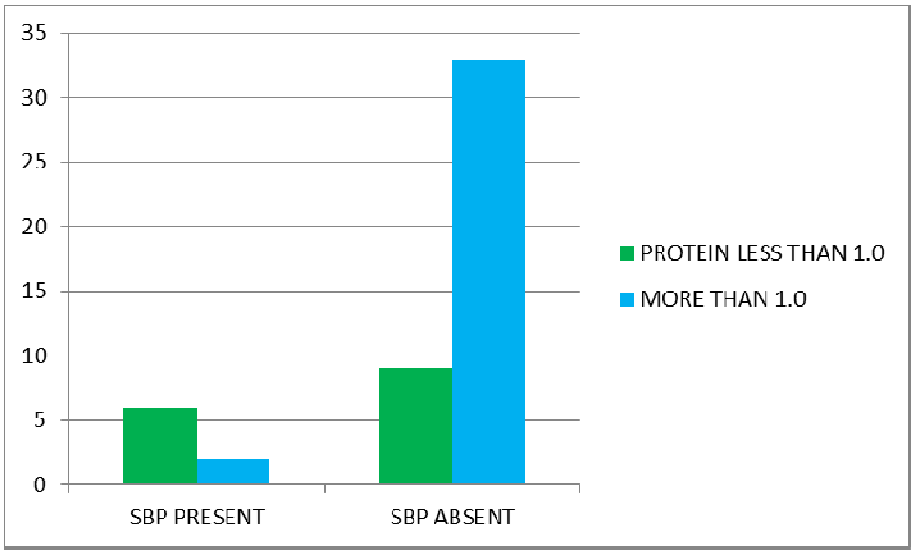


Chart 8. Corelation between protein level ascitic fluid and SBP

			Ascitic fluid		Total
			1	2	
SBP	1.00	Count	5	3	8
		% within SBP	62.5%	37.5%	100.0%
		% within Ascitic fluid	100.0%	6.7%	16.0%
	2.00	Count	0	42	42
		% within SBP	0.0%	100.0%	100.0%
		% within Ascitic fluid	0.0%	93.3%	84.0%
Total		Count	5	45	50
		% within SBP	10.0%	90.0%	100.0%
		% within Ascitic fluid	100.0%	100.0%	100.0%

Table 3. Chi – Square chart showing significant in protein level in ascitic fluid

After calculating the co relation between the child pugh classification and the prevalence of SBP it was found to be significant at $p < 0.05$

Table 4. Corelation between Child Pugh's classification with SBP

	SBP PRESENT	**SBP ABSENT**
CLASS C	3	2
CLASS B & A	5	40

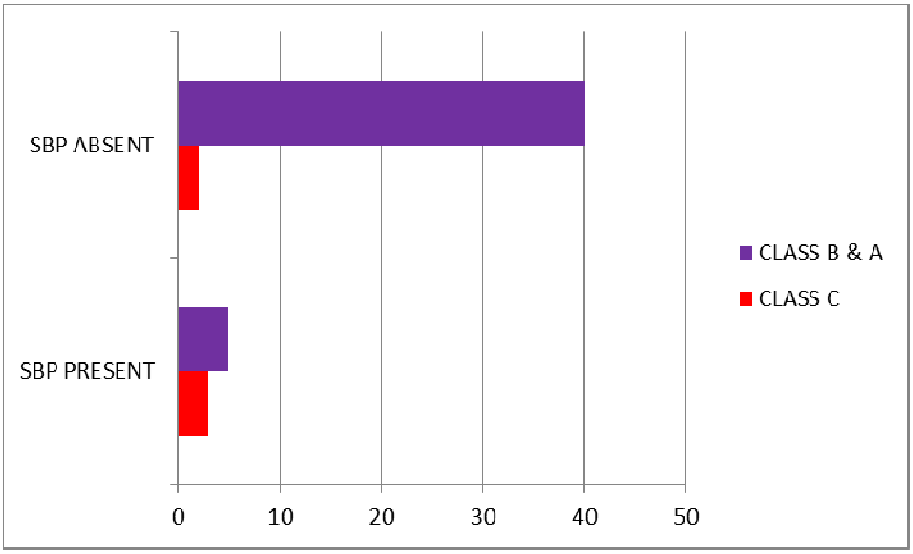


Chart 9. Corelation between Child Pugh's Classification and SBP

As it was found in the previous studies, there is a strong link between the child pughs scoring and the development of SBP .

The rise in serum bilirubin and its correlation with the occurrence of SBP was also studied but it was found to have no significance.

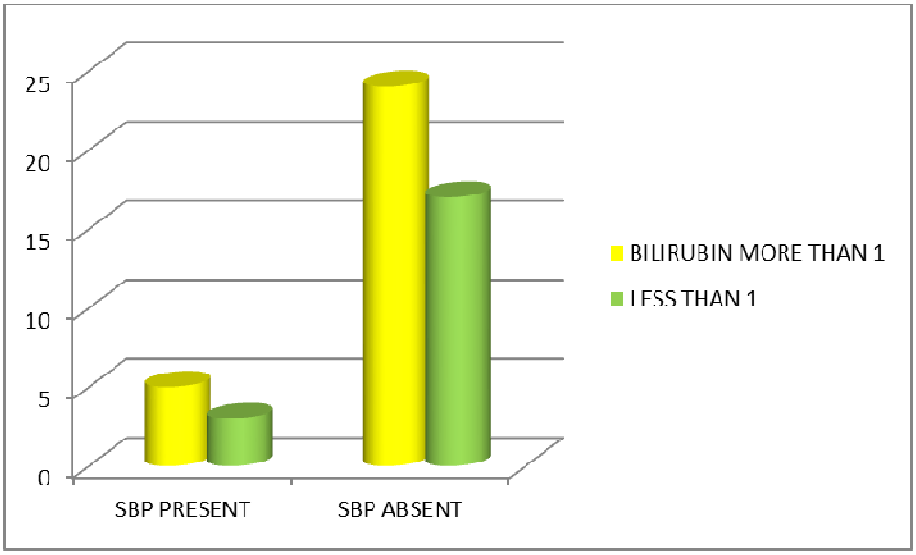


Chart 10. Corelation between Serum bilirubin with SBP

Another comparative study was with the occurance of SBP among alcoholics . The co relation was not significant.

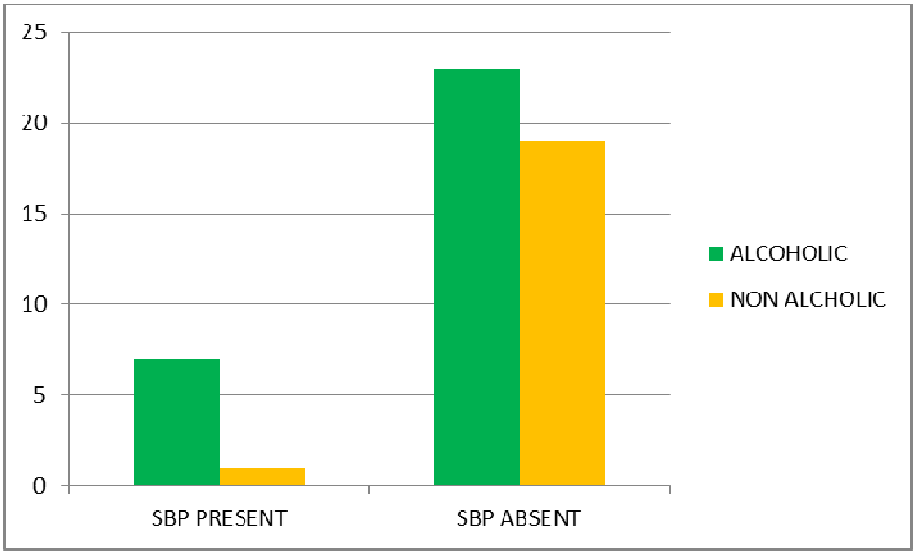


Chart 11. Corelation between alcoholics and SBP

If taken as separate, among the SBP the ones with culture positive i.e bacterascites and those with cell count more than 250, the following conclusions were made

Protein level in ascitic fluid

Table 5.Comparison between culture positive and high cell count with protein level in ascitic fluid

	CULTURE POSITIVE alone	**HIGH CELL COUNT**	**BOTH PRESENT**
PROTEIN LESS THAN 1.0	2	2	2
MORE THAN 1.0	1	1	0

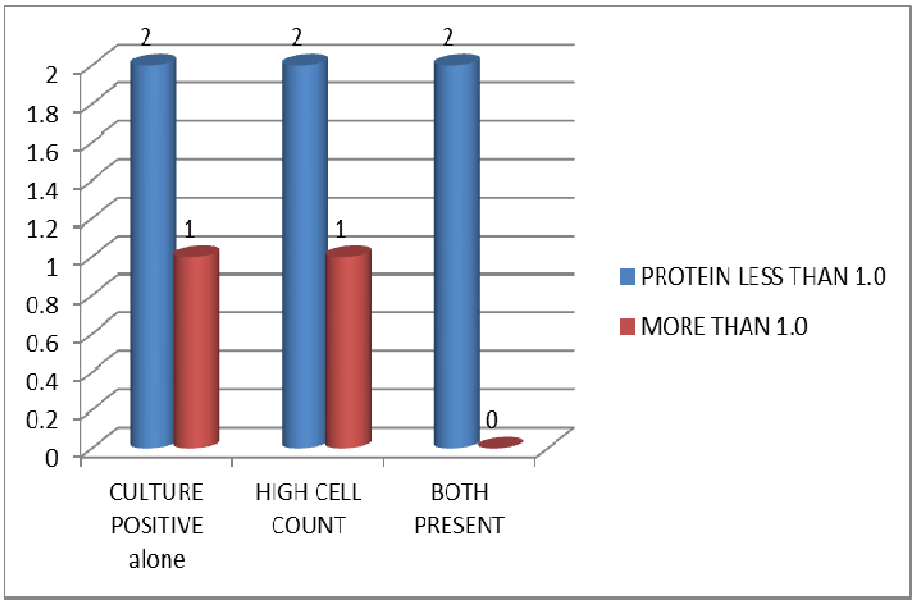


Chart 12. Comparison study with culture positive and high cell count.

Child Pugh Classification

Table 6. Comparitive study between culture positive and high cell count with Child Pugh's Classification

	CULTURE POSITIVE alone	**HIGH CELL COUNT**	**BOTH PRESENT**
CLASS C	2	0	1
CLASS B & A	1	2	2

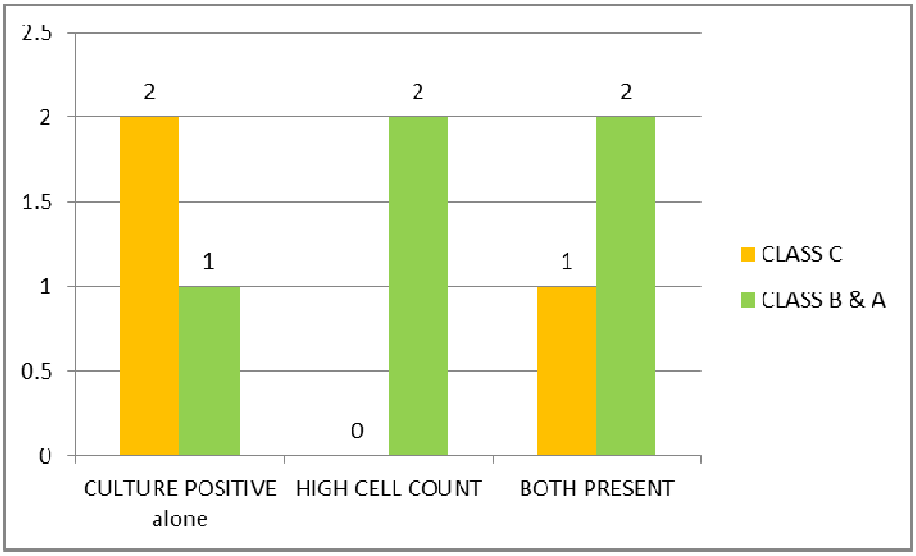


Chart 13. Comparitive study between culture positive and high cell count with Child Pugh's Classification

Bilirubin

Table 7. Comparitive study between culture positive and high cell count with Serum Bilirubin

	CULTURE POSITIVE alone	**HIGH CELL COUNT**	**BOTH PRESENT**
BILIRUBIN MORE THAN 1	3	1	1
LESS THAN 1	0	2	1

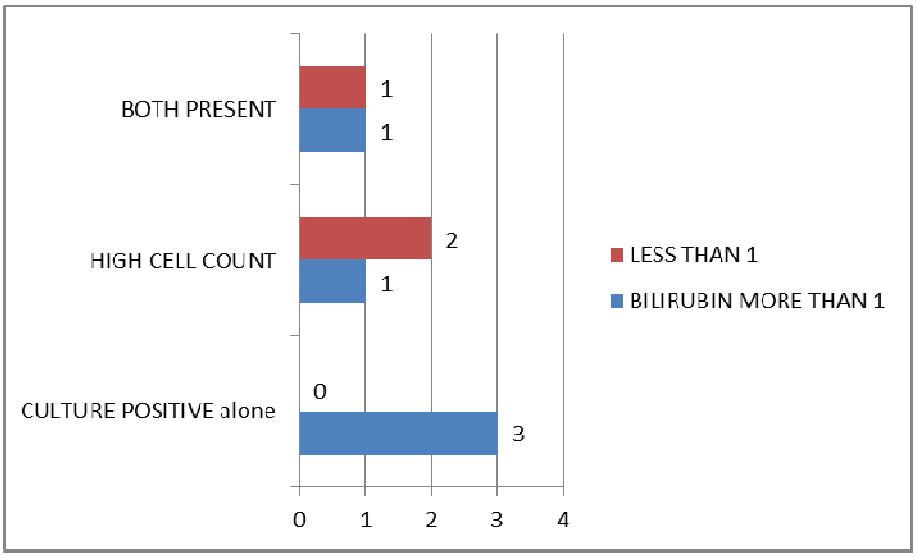


Chart 14. Comparitive study between culture positive and high cell count with Serum bilirubin

Alcoholism

Table 8. Comparitive study between culture positive and high cell count with Alcoholism

	CULTURE POSITIVE	**HIGH CELL COUNT**	**BOTH PRESENT**
ALCOHOLIC	3	1	3
NON ALCOHOLIC	0	1	0

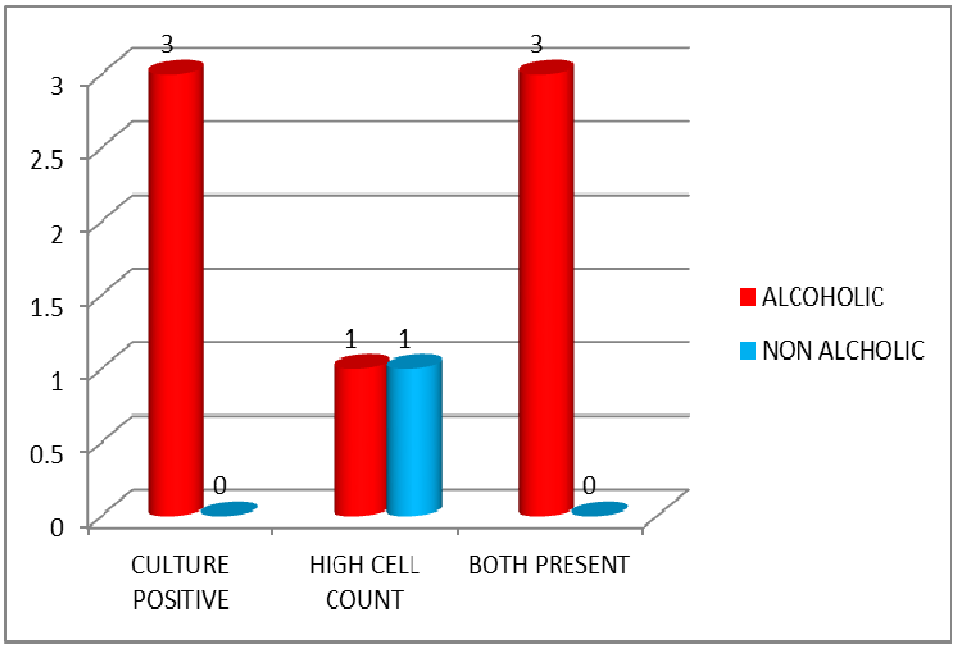


Chart 15. Comparitive study between culture positive and high cell count with Alcoholism

Other parameters that were studied are as follows

Serum protein level

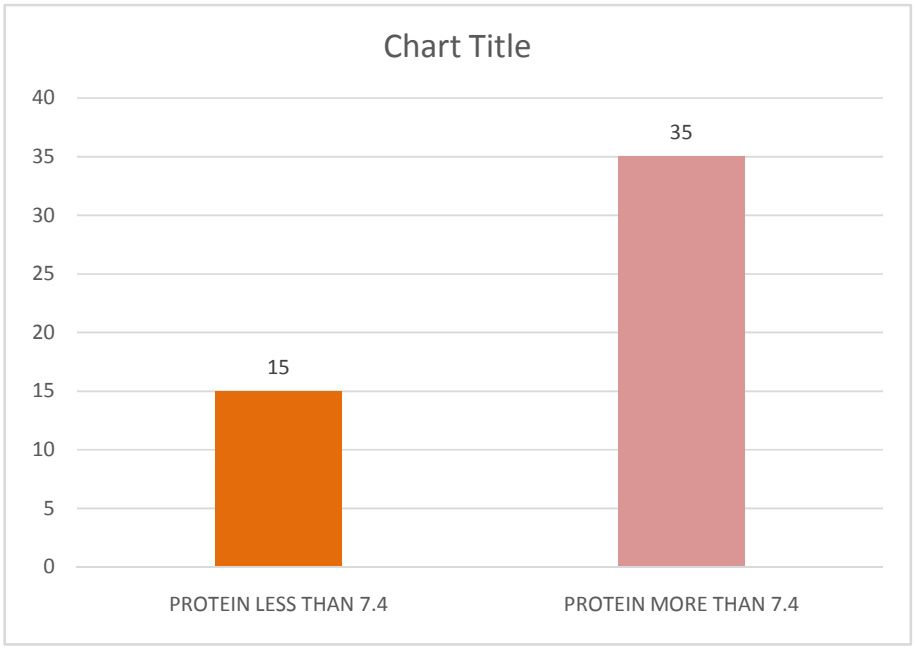


Chart 16. Serum protein level in the study population

Serum bilirubin levels were depicted as below 1 mg / dl and above

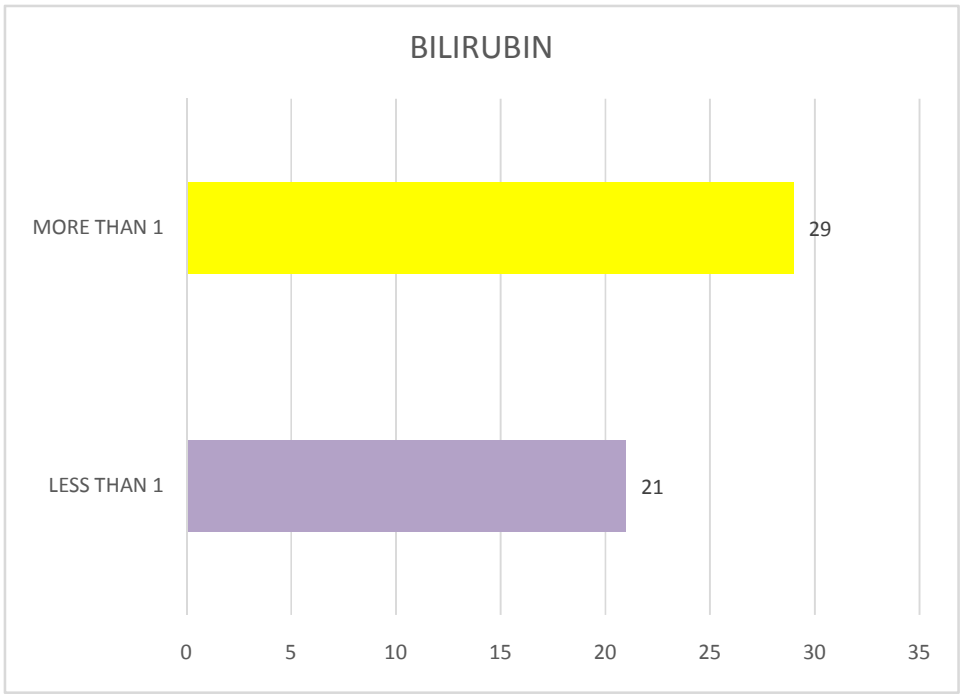


Chart 17. Serum Bilirubin in the study population

Serum amylase in IU /l

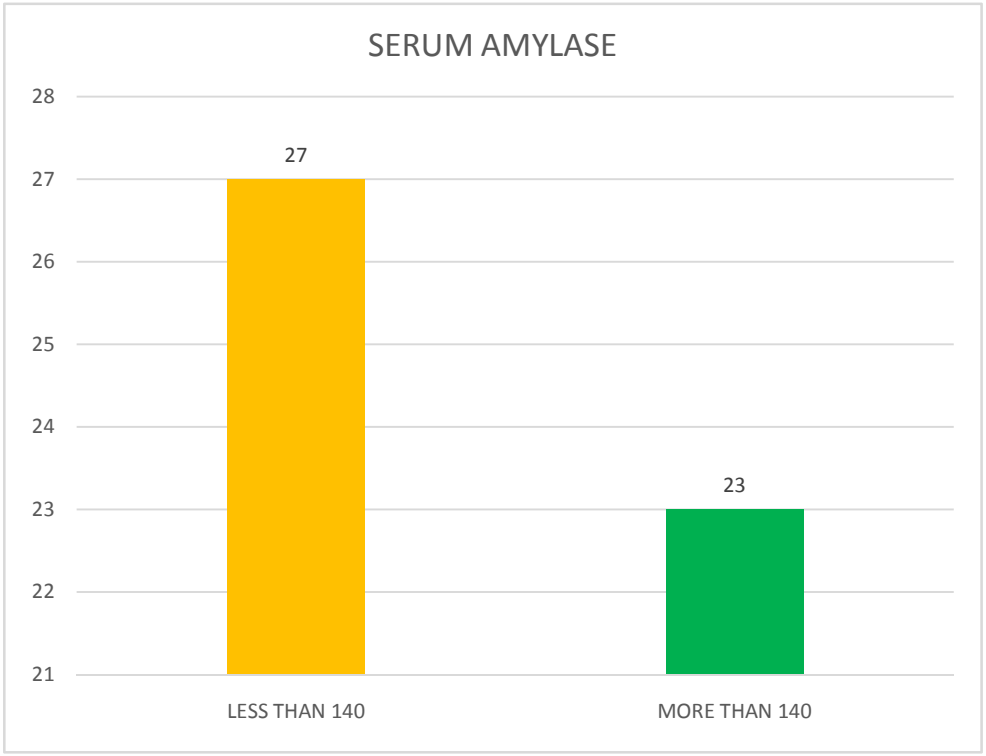


Chart 18 . Serum Amylase in the study population

SGOT

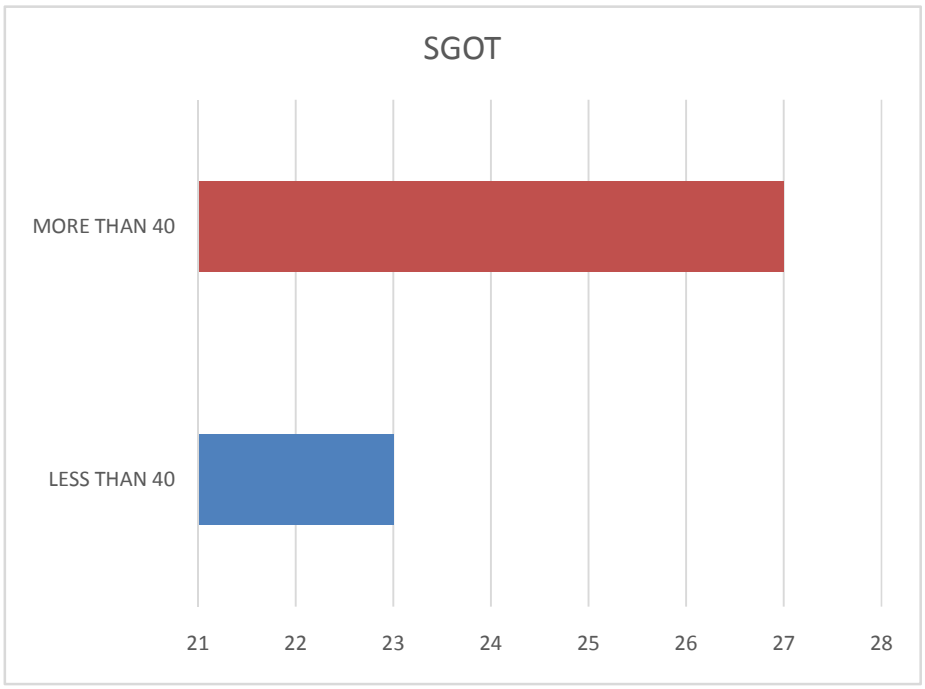


Chart 19 . Serum SGOT level in the population

SGPT

Chart 20 . Serum SGPT level in the study population

DISCUSSION

Spontaneous Bacterial Peritonitis is a life threatening complication that is characterised by an infection of the ascitic fluid in the absence of any foci of inflammation . So a prompt diagnosis of the disease is very necessary as the mortality of the disease is very high if not intervened at the right time.

The study conducted at Coimbatore Medical College regarding the prevalence of Asymptomatic Spontaneous Bacterial Peritonitis was done for a period of 1 year. 50 cases were selected according to the inclusion and exclusion criteria. The samples were analysed with strict confidentiality and the results were also considered the same.

Among the patients studied, majority of the study population were consisting of males. Also it was found that the around 60 % of the study population were alcoholics irrespective of the sex. The duration of cirrhosis was also varying and as the charts shown above, the duration of the cirrhosis has no correlation to the occurrence of SBP.

With respect to the cell count, only 5 of the study population had a count of more than 250 /cu.mm . The highest value recorded among the study population was 600 / cu.mm. The lowest was recorded as 2 cells . So , only 10 % of the patients had Culture Negative Neutrocytic Ascites(CNNA).

The culture study trend showed that majority were gram negative bacilli, E.coli being the most common seen on 4 out of the 6 culture positive analysis . The other two were Klebsiella pneumonia and Streptoccocus.

As the case defining criteria was fulfilment of any one ie cell count more than 250 /cu.mm or culture positivity, 8 cases fulfilled the criteria and so the prevalence of Asymptomatic SBP was as low as 16 %.

Patients coagulation status was also judged by analysing the PT time. With the multiple parameters, The Child pughs criteria was calculated and the patients were classified . Majority of the cases came in the Class B with 32 patients. Class A was occupied by 13 patients and Class C by 5 patients.

The bilirubin levels were found to be almost equally distributed with 29 patients showing hyperbilirubinemia and 21 patients with normal bilirubin levels

Next some other parameters were correlated . Firstly as mentioned in the literatures, the ascitic fluid protein level has a strong predilection for contracting infection due to the decreased action of the reticuloendithelal system and the reduced opsonin level in the fluid . In our study, by correlating using the Chi- square technique, the correlation was significant at $p < 0.05$

In the study, it was found that among the 8 positive for SBP 5 had protein level less than 1 g/dl . So comparing with the protein level of non SBP

cases , the values were significant and hence considered to be having a positive correlation .

Next to be considered was the Child Pugh's score and its correlation with SBP. As mentioned in various literature, the severity of Child Pugh's score has a strong predilection in formation and worsening of SBP. In our study the number of cases with Child Pugh's score as Class C were 5.Among the 8 who had SBP, 3 were in Class C prognostic index and thereby was significant at p value less than 0.05.

The 60 % of the population who were alcoholics had not abstained from alcohol. But there was no significant link between the pathogenesis or rather the occurrence of SBP as the non SBP group also was having a lot of alcoholics. Alcoholism per se do not aggravate the risk of developing SBP. But following a bout of alcohol, severe retching leading to Mallory Weiss tear or a bout of hematemesis can lead to SBP. Also another complication i.e aspiration pneumonia can precipitate SBP.

High bilirubin notes in roughly 60 % of the patients had no direct impact on the load of SBP as the hyperbilirubinemia was found in more number in patients without SBP too and hence proven to be not significant . But it has an indirect correlation as it has been incorporated into the Child pugh"s criteria .

To rule out other causes of infection, serum amylase levels were studied in all the cases. But the level was minimal and it had no direct link or its raised value do not point towards SBP.

Now taking into consideration about the individual case of SBP i.e ones with cell count more than 250 and those with culture , some more deductions were made

In correlation to the protein level in ascitic fluid , when taking culture alone 2 of the 3 patients were having it less than 1 g/dl . But when cell count is taken, 2 of the 3 patients were having it less than 1 g/dl . When both are positive, all the 2 had protein less than 1 g/dl.

Next in line is the Child Pugh's Classification. Among the culture positive , 2 out of 3 were in Class C . In the cell count criteria none were in class C but when combined 1 out of the 3 were in Class C .

Bilirubin study revealed that all the 3 of the culture positive patients were having bilirubin more than 1 , high cell count 1 out of 3 were showing high bilirubin and when both are positive 1 out of 2 were having hyperbilirubinemia.

Alcoholism and correlation with the SBP variants were as follows . All the culture positive patients were alcoholic, 1 of the 2 high cell count variant was an alcoholic and when combined again all of them were alcoholics .

All the patients had started to receive antibiotics after the paracentesis as the risk of iatrogenic infection was a significant one . After the results came out , the definitive management was given i.e Inj . Cefotaxime 2 g i.v TDS . The patients drastically improved .

The patients with Child Pugh score as Class C were also given other supportive measures after the samples were taken as intervening with treatment measures prior to it might alter the outcome of the disease . after the sample collection , they were administered with clotting factors and albumin infusion . Patients drastically improved.

As seen in the study , the various other parameters like the transaminases had no relation with the disease outcome . In none of the cases , the transaminases were significantly raised . Transaminases are raised only in states of acute liver injury and none of the study individuals were expected to have the same .

Other measures like the usage of L-ornithine and L- aspartate could have been used but none of the patients were in hepatic encephalopathy and so it was not used in the intervention .

All the patients were under regular follow up after 2 weeks . None of them had complications . All the patients drastically improved with the treatment and there was no mortality noted .

SUMMARY

Spontaneous Bacterial Peritonitis is a dreaded complication of cirrhosis of liver . The main pathophysiology attributed to the disease is the translocation of the gut microbes via the mysentric lymph nodes that gain access to the peritoneal cavity. The term SBP was coined by Fennel . The most common organism attributed to the infection is E. coli . To generalise Gram negative bacilli occupy the majority of the pathogenic organism with Gram positive cocci next and lastly by Anerobic organism .

The mortality of this disease is very high . The in hospital mortality ranges from 10 to 30 %. Before the advent of antibiotics , the mortality was as high as 90 % .

The study was conducted in our hospital in patients admitted in the medical and gastroenterology ward . 50 patients were selected after scrutiny . The ascitic fluid analysis was done . Patients were started on prophylactic antibiotics after the therapy . There was no mortality in the study group during the study .

Among the 50 patients only 8 patients were found to have SBP which brings the prevalence up to 16 % . The patients with cell count more than 250 were 5 and the culture positive cases were 6 among the population . The Child pugh scoring was made in the patients and it was seen that 32 patients came in the Class B , 5 came in Class C and the rest of the 13 were in Class A .

The serum bilirubin and the transaminases levels showed no strong correlation with the incidence of SBP .

The protein level in the ascitic fluid and the occurrence of SBP was well correlated in our study . Out of the 8 patients 5 of the patients had low protein level of less than 1 g/dl which was significant by chi – square chart with p value less than 0.05 .

Also it was found that there is a strong correlation in the child pugh criteria and the incidence of SBP. Among the patients 8 patients, 3 were in Class C according to the child pugh's criteria. This when analysed statistically, it showed significance at $p<0.05$.

So to conclude, the prevelance of SBP is low in our institution and SBP has correlation with low protein in ascitic fluid and Child Pugh criteria .

CONCLUSION

The study regarding the prevalence of Asymptomatic Spontaneous Bacterial Peritonitis was conducted during the period of July 2014 to July 2015. The ascitic fluid were examined and the results were analysed . After the analysis , we have come to a conclusion that the prevalence of SBP is very low at **16%** . There is also a strong correlation between low ascitic fluid protein level (<1g/dl) and SBP.Among the study population, the majority of the patients with SBP had Child Pugh's criteria in Class C. This was also correlated well in our study .

So to conclude, the prevalence of Asymptomatic Spontaneous Bacterial Peritonitis is low is known cirrhotic patients with ascites .

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PROFORMA

1. NAME :
2. AGE :
3. SEX :
4. WHETHER HE/SHE IS
   SUFFERING FROM FEVER
   DURING THE LAST 2 WEEKS : YES/NO
5. WHETHER HE /SHE IS ON
   PROPHYLACTIC ANTIBIOTICS : YES/NO
6. WHETHER USG IS PRIORLY TAKEN : YES/NO
   IF YES, FINDINGS :
7. WHETHER HE/SHE IS HAVING
   ALTERED SLEEP PATTERN : YES/NO
8. WHETHER ALCOHOL : YES /NO
9. DURATION OF CIRRHOSIS :
10. WHETHER CONSENT IS TAKEN : YES/NO
11. AMOUNT OF FLUID COLLECTED :
12. COLOUR OF FLUID :
13. NUMBER OF NEUTROPHILS :
14. CULTURE REPORT :
15. BIOCHEMICAL ANALYSIS
    a. Sugar :
    b. Protein :
16. LIVER FUNCTION TEST :
17. PROTHROMBIN TIME :
18. SERUM AMYLASE :
19. FINAL INTERPRETATION :

CONSENT FORM

You, Shri./ Smt./ Kum. _____, aged ____ years, S/o / D/o / W/o _____, residing at _____ _____ are requested to be a participant in the research study titled '*Detection of Spontaneous Bacterial Peritonitis in asymptomatic cirrhotic patients with ascites attending OPD*' in Government Medical College Hospital, Coimbatore, conducted by Dr. Joe Francis Mathew, Post Graduate Student in the Department of General Medicine, Coimbatore Medical College. You satisfy eligibility criteria as per the inclusion criteria. You can ask any question or seek any clarifications on the study that you may have before agreeing to participate.

RESEARCH BEING DONE

Detection of Spontaneous Bacterial Peritonitis in asymptomatic cirrhotic patients with ascites attending OPD'

PURPOSE OF RESEARCH

1. Early detection of Spontaneous Bacterial Peritonitis in patients with Ascites who do not have classical symptoms of the same
2. To intervene in positive cases prior to onset of complications.

PROCEDURES INVOLVED

Collection of ascitic fluid from the patients for biochemical , culture and cell count study.

DECLINE FROM PARTICIPATION

You are hereby made aware that participation in this study is purely voluntary and honorary and that you have the option and the right to decline from participation in the study.

PRIVACY AND CONFIDENTIALITY

You are hereby assured about your privacy. Privacy of subject will be respected and any information about you or provided by you during the study will be kept strictly confidential.

AUTHORIZATION TO PUBLISH RESULTS

Results of the study may be published for scientific purposes and/or presented to scientific groups, however you will not be identified; neither will your privacy be breached.

STATEMENT OF CONSENT

I, _____, do hereby volunteer and consent to participate in this study being conducted by Dr. Joe Francis Mathew. I have read and understood the consent form / or it has been read and explained to me. The study has been fully explained to me, and I may ask questions at any time.

Signature / Left Thumb Impression of the Volunteer Date:

Signature and Name of witness Date:

ABBREVIATION FOR MASTER CHART

1. PML – Poly Morphonuclear Leucocyte
2. A – Albumin
3. G- Globulin
4. PT – Prothrombin Time
5. Bili – Bilirubin
6. M-Male
7. F-Female

name	age	sex	alcohol	Duration of cirrhosis (yrs)	Ascitic fluid					s. bili	Sgot	Sgpt	S protein		amylase		
					Cell count (PML)/mm^3	culture	Biochemistry						A g/dl	G g/dl			
							sugar	Protein								PT(sec)	Child's Pugh score
								A g/dl	G g/dl								
1. Abdul Sukoor	62	M	N	9	20	NEGATIVE	68	0.3	0.1	2.6	28	24	2.5	4.2	110	40	C
2. Mariyammal	85	F	N	10	18	NEGATIVE	80	1.8	1.3	1.5	36	43	3.5	3.2	34	18.4	A
3.Thangaru	53	F	N	7	2	NEGATIVE	67	0.7	1.0	0.7	23	24	2.8	3.4	65	20.4	B
4. Ramasamy	52	M	Y	5	112	NEGATIVE	64	1.1	0.9	1.4	46	57	3.0	3.0	64	13.6	B
5. Achiyammal	74	F	Y	10	222	POSITIVE	56	0.5	0.3	3.8	30	45	2.6	4.0	143	28.3	C
6. Salim	35	M	N	6	32	NEGATIVE	73	1.4	1.2	1.2	47	42	3.4	3.1	74	15.8	A
7 .Rangaraj	55	M	Y	9	10	NEGATIVE	66	0.9	0.4	0.4	20	24	3.0	3.2	52	24.4	B
8. Udayashankar	33	M	Y	7	20	NEGATIVE	64	0.5	0.8	1.8	56	45	3.8	3.4	48	20.8	B
9. Sarojini	45	F	N	2	45	NEGATIVE	72	0.5	0.3	2	35	45	3.0	3.8	150	18.4	B
10. Nagendran	45	M	Y	7	8	NEGATIVE	48	0.4	0.2	0.9	20	17	3.0	3.0	32	17.5	B
11. Sulochana	49	F	N	5	50	NEGATIVE	42	1.8	1.0	0.6	35	20	3.8	3.1	117	19.1	A
12. Pathma	50	F	N	8	56	NEGATIVE	118	1	1.1	1.7	30	42	3.5	3.6	134	23.5	A
13. Sivalingam	50	M	Y	3	4	NEGATIVE	80	0.4	0.1	0.3	80	78	2.9	3.2	122	22.3	B
14Saroja	48	F	N	6	10	NEGATIVE	75	1.2	1.0	0.9	40	60	3.0	3.1	132	20.5	B
15Narasimgam	58	M	Y	7	58	NEGATIVE	97	0.8	0.6	1	56	54	2.8	2.1	144	23.1	B
16Manoharan	58	M	Y	4	14	NEGATIVE	80	1.0	0.4	1.8	58	53	3.0	3.0	184	21	B
17Rajan	44	M	Y	3	24	NEGATIVE	85	1.2	0.5	0.8	68	59	2.9	3.2	173	20.6	B
18Karpathal	40	F	N	4	45	NEGATIVE	73	0.9	0.6	0.5	90	79	1.8	3.3	162	20.3	B
19Pappamal	58	F	N	7	84	NEGATIVE	50	0.5	0.3	0.2	100	120	3.8	3.0	145	24	A
20Selvi	45	F	N	2	20	NEGATIVE	98	0.6	0.3	2.6	38	40	2.4	4.1	125	18	B
21 Mani	60	M	Y	7	16	NEGATIVE	67	1.0	0.8	1.7	40	36	2.5	3.5	169	17.8	B
22Rajamani	52	F	N	2	24	NEGATIVE	57	0.4	0.1	0.7	50	60	2.0	4.6	157	19	B
23Pothundi	58	F	Y	8	40	NEGATIVE	89	1.6	1.0	0.8	90	87	2.8	2.4	197	18.4	B
24 Raja	34	M	Y	5	40	NEGATIVE	73	0.8	0.6	0.9	40	48	3.6	3.1	138	16	A
25Dharani	40	F	N	4	8	NEGATIVE	40	1.0	0.8	1.1	30	26	3.8	3.6	165	18	A
26Kaliyammal	60	F	N	3	170	NEGATIVE	50	1.5	1.3	1.9	56	32	3.1	3.0	142	21.5	B
27Kandasamy	50	M	N	5	24	NEGATIVE	96	0.6	0.9	1.3	28	26	3.0	4.0	156	22	B
28Rana	43	M	Y	3	120	POSITIVE	30	0.8	0.3	1.2	35	67	2.8	4.0	23	27	B
29Veliammal	65	F	N	8	80	NEGATIVE	78	1.5	1.1	0.8	60	80	3.9	3.6	167	20.3	A

30Vadivel	30	M	Y	4	48	NEGATIVE	60	1.0	1.2	4.6	80	110	2.4	4.2	178	22	C
31Ragar	45	M	Y	6	60	NEGATIVE	56	0.5	0.1	0.3	40	34	3.1	2.8	128	26.4	B
32Arun	27	M	N	2	540	NEGATIVE	78	0.6	0.2	0.9	17	21	2.2	2.4	147	21.5	B
33 Krishnan	32	M	Y	3	380	POSITIVE	70	0.5	0.3	2.7	110	140	2.2	3.8	173	30.3	C
34Eswaramoorthy	58	M	N	7	72	NEGATIVE	54	1.5	1.0	1	90	82	2.5	3.1	134	19	B
35Jayaraj	66	M	Y	5	600	NEGATIVE	74	1.2	0.6	1.9	56	48	2.9	4.8	160	17.3	B
36 Aran	64	M	Y	7	120	NEGATIVE	80	0.9	0.5	1.6	76	50	2.9	4.2	156	21	B
37Nandakumar	38	M	Y	3	28	NEGATIVE	84	1.2	0.9	1.3	87	69	3.0	3.8	134	22	B
38 Ganesh	45	M	Y	4	50	NEGATIVE	60	0.8	0.3	1.4	46	56	3.7	2.8	130	25	A
39Jayanthi	35	F	N	3	12	NEGATIVE	73	1.4	2.0	0.5	98	67	2	2.2	169	17.2	B
40 Ramesh	45	M	Y	4	10	NEGATIVE	79	0.4	0.1	0.6	57	40	3.8	2.6	78	19.5	A
41Murugan	45	M	Y	5	100	NEGATIVE	84	1.2	0.7	0.9	80	75	3.5	3.9	68	20	A
42Sneha	14	F	N	2	64	NEGATIVE	81	0.9	0.3	1.3	57	50	2	2.5	90	23	B
43Laxmanan	38	M	Y	1	32	NEGATIVE	70	1.3	0.9	1.5	68	60	2.9	2.6	68	22.9	B
44Manoharan	64	M	Y	4	32	NEGATIVE	90	1.3	1.2	1.4	68	90	4.0	3.2	155	25	A
45Shekar	43	M	Y	7	4	NEGATIVE	136	0.4	0.6	0.9	40	45	3.5	3.2	136	28	B
46Vishwanathan	39	M	Y	2	96	NEGATIVE	64	1.8	1.3	0.7	35	68	4.0	3.8	143	19	A
47Mohanraj	55	M	Y	8	540	POSITIVE	68	0.7	0.2	0.7	30	23	2.5	3.6	55	27	B
48Babu	40	M	Y	4	280	POSITIVE	80	0.2	0.3	1.0	55	40	2.2	4.0	150	26	B
49Yuvaraj	52	M	Y	3	5	NEGATIVE	90	0.4	0.6	1.2	40	40	2.9	2.5	128	24.4	B
50 Ajay paul	27	M	Y	3	231	POSITIVE	72	0.8	0.2	2.0	40	30	2.6	3.2	123	39.1	C

ஒப்புதல் படிவம்

பெயர் :

பாலினம் :

முகவரி : வயது :

அரசு கோவை மருத்துவக் கல்லூரியில் பொது மருத்துவம் மருத்துவ துறையில் பட்ட மேற்படிப்பு பயிலும் மாணவர் _____ அவர்கள் _____ ஆய்வில் மேற்கோள்ளும் செய்முறை மற்றும் அனைத்து விவரங்களையும் கேட்டுக் கொண்டு எனது சந்தேகங்களை தெளிவுபடுத்திக் கொண்டேன் என்பதை தெரிவித்துக் கொள்கிறேன்.

நான் இந்த ஆய்வில் முழு சம்மதத்துடன், சுய சிந்தனையுடனும் கலந்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் என்னுடைய அனைத்து விபரங்கள் பாதுகாக்கப்படுவதுடன் இதன் முடிவுகள் ஆய்விதழில் வெளியிடப்படுவதில் ஆட்சேபனை இல்லை என்பதை தெரிவித்துக்கொள்கிறேன். எந்த நேரத்தில் அந்த ஆய்விலிருந்து நான் விலகிக் கொள்ள எனக்கு உரிமை உண்டு என்பதையும் அறிவேன்.

இடம் : கையொப்பம் / ரேகை

நாள் :